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Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials[†]

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We investigate whether private research investments are distorted away from long-term projects. Our theoretical model highlights two potential sources of this distortion: short-termism and the fixed patent term. Our empirical context is cancer research, where clinical trials—and hence, project durations—are shorter for late-stage cancer treatments relative to early-stage treatments or cancer prevention. Using newly constructed data, we document several sources of evidence that together show private research investments are distorted away from long-term projects. The value of life-years at stake appears large. We analyze three potential policy responses: surrogate (non-mortality) clinical-trial endpoints, targeted R&D subsidies, and patent design. (*JEL* D92, G31, I11, L65, O31, O34)

Over the last five years, eight new drugs have been approved to treat lung cancer, the leading cause of US cancer deaths.[1] All eight drugs targeted patients with the most advanced form of lung cancer, and were approved on the basis of evidence that the drugs generated incremental improvements in survival. A well-known example

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[1] See the lists of US Food and Drug Administration (FDA) approved hematology/oncology drugs by year: http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

is Genentech's drug Avastin, which was estimated to extend the life of late-stage lung cancer patients from 10.3 months to 12.3 months.[2] In contrast, no drug has ever been approved to prevent lung cancer, and only six drugs have ever been approved to prevent any type of cancer. While this pattern could solely reflect market demand or scientific challenges, in this paper we investigate an alternative hypothesis: private firms may invest more in late-stage cancer drugs—and *too little* in early-stage cancer and cancer prevention drugs—because late-stage cancer drugs can be brought to market comparatively quickly, whereas drugs to treat early-stage cancer and to prevent cancer require a much longer time to bring to market. More broadly stated, we investigate whether private firms differentially underinvest in long-term research, by which we mean technologies with long time lags between the initial spark of an idea and the availability of a commercially viable product. We document evidence that such underinvestment is quantitatively significant in an important context—treatments for cancer—and analyze potential policy responses.

The idea that companies may be excessively focused on behaviors with short-run payoffs is an old one. A large policy- and practitioner-oriented literature has conjectured that managers may maximize short-term rather than long-term firm value (Porter 1992a,b; National Academy of Engineering 1992). In the academic literature, Stein (1989) and others have argued that firms may be more impatient than neoclassical models would predict due to frictions such as agency problems within the firm. While such corporate short-termism has been widely discussed, little empirical evidence exists to either support or refute this view (see Stein 2003 for a survey and Asker, Farre-Mensa, and Ljungqvist 2015 for a more recent contribution).

We propose an additional reason why private firms may be particularly likely to focus on the short term in the context of research and development (R&D): the structure of the patent system.[3] Patents award innovators a fixed period of market exclusivity (e.g., 20 years in the United States). Yet, since in many industries firms file patents at the time of discovery ("invention") rather than first sale ("commercialization"), *effective* patent terms vary: inventions that commercialize at the time of invention receive a full patent term, whereas inventions that have a long time lag between invention and commercialization receive substantially reduced—or in extreme cases, zero—effective patent terms. This means that the patent system provides, perhaps inadvertently, very little incentive for private firms to engage in long-term research.[4] Our theoretical model clarifies that, in fact, there is a sense in which

[2] Specifically, Avastin was approved for "unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC [non-small cell lung cancer]" patients and the clinical trial effectiveness estimate is posted on the Genentech website: http://www.gene.com/media/product-information/avastin-lung. As noted on the website, this is the first drug to extend median survival time for this patient population beyond 1 year.

[3] While the importance of patents has been debated in many industries, given our empirical focus on the pharmaceutical industry it is worth noting that a variety of evidence suggests that patents play a key role in motivating innovation in the pharmaceutical industry, including industry interviews (Mansfield, Schwartz, and Wagner 1981; Mansfield 1986; Levin et al. 1987; Cohen, Nelson, and Walsh 2000), the cost structure of new drug development relative to the generic production (DiMasi, Hansen, and Grabowski 2003; Adams and Brantner 2006; Wroblewski et al. 2009), and the fact that standard investment models used by pharmaceutical firms pay close attention to effective patent length (Mayer Brown 2009). Informal interviews we conducted with venture capitalists for this paper also support this view, in the sense that these interviews highlighted the fixed term structure of the patent system as something that has important effects on research investments (see online Appendix C).

[4] It has long been recognized that heterogeneity across inventions—such as variation in risk-adjusted costs of development—implies that any given fixed patent term will award "too much" market exclusivity to some inventions, and will be insufficient to motivate the development of others; on optimal patent length and optimal

corporate short-termism and fixed patent terms reinforce each other in distorting private research dollars away from long-term investments. The fixed patent term reduces the number of calendar years for which private firms enjoy monopoly protection on investments, and excess discounting reduces the weight the private firm places on each of those years relative to the societal weight.

The idea that firms may underinvest in long-term research, while intuitive, is difficult to test empirically. The key prediction is that there is "missing" private R&D on scientifically feasible projects that would be developed but for their long commercialization lags. In practice, we do not observe the commercialization lags of projects that are never developed, and "missing" private R&D is hard to distinguish from alternative explanations such as a lack of market demand or a lack of scientific opportunities.

Two features of cancer markets allow us to make progress on quantifying this missing R&D. First, the treatment of cancer patients is organized around the organ (e.g., lung) and stage (e.g., metastatic) of disease, which provides a natural categorization of both observed and potential R&D activity. Second, for each such group of cancer patients we observe a good predictor of how long it would take to commercialize drugs for those patients: survival time. Survival time predicts commercialization lags because a firm commercializing a new cancer drug must complete FDA-required clinical trials showing evidence that the drug is safe and effective; and, for cancer clinical trials, "effective" is usually interpreted as improving survival.[5]

To illustrate, consider two examples of clinical trials for prostate cancer treatments, both published in the *New England Journal of Medicine* in 2011. A first study, de Bono et al. (2011), analyzed a treatment for metastatic prostate cancer (an advanced stage of prostate cancer with a five-year survival rate on the order of 20 percent). The study tracked patient survival for a median time of 12.8 months, and estimated statistically significant improvements in survival (a gain of 3.9 months of life). A second study, Jones et al. (2011), analyzed a treatment for localized prostate cancer (an early stage of prostate cancer with a five-year survival rate on the order of 80 percent). The study tracked patient survival for a median time of 9.1 years, estimating statistically significant improvements in survival. As expected, this stark difference in patient follow-up times translates into a large difference in clinical trial length: 3 years for the metastatic patient trial versus 18 years for the localized patient trial. Consistent with the idea that commercialization lags differentially reduce private R&D incentives, the study of metastatic cancer patients was funded by a private firm (Cougar Biotechnology) whereas the study of localized cancer patients was funded by the National Cancer Institute.

We construct data on all clinical trials for cancer treatments over the period 1973–2011, which we match to data on patient survival times over the same period. Our survival data is drawn from patient-level cancer registry data, which we aggregate to cancer-stage-level patient groups. Our measure of cancer treatment R&D is newly constructed from a clinical trial registry that has cataloged cancer clinical

patent breadth see, e.g., Machlup (1958); Nordhaus (1969, 1972); Scherer (1972); Kaplow (1984); Gilbert and Shapiro (1990); Klemperer (1990); and Scotchmer (1991). Relative to this literature, the patent analysis in our model highlights a simple—and, we think, important—specific form of heterogeneity in patent-provided incentives arising from commercialization lags that has potentially important consequences for welfare.

[5] There are exceptions to this general statement, which our empirical work will take advantage of.

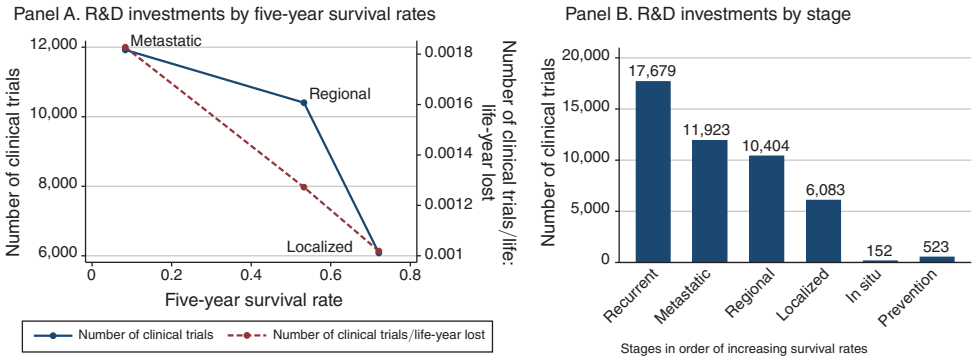

FIGURE 1. SURVIVAL TIME AND R&D INVESTMENTS: STAGE-LEVEL DATA

Notes: This figure plots measures of clinical trial activity for each stage of cancer from 1973 to 2011. Panel A plots two measures of clinical trial activity for each stage of cancer from 1973 to 2011 against five-year survival rate among patients diagnosed with each stage between 1973–2004 (the cohorts for which five-year survival is uncensored). The left-hand-side axis plots the number of clinical trials enrolling patients of each stage from 1973 to 2011. The right-hand-side axis plots the number of clinical trials enrolling patients of each stage from 1973 to 2011 divided by number of life-years lost—measured as age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied by market size. Panel B is a bar chart plotting the same data for localized, regional, and metastatic cancers, but also including the number of trials for preventive technologies as well as in situ and recurrent cancers. For details on the sample, see the text and online Data Appendix.

trials since the 1970s. The key feature of these R&D data which enables our analysis is that for each clinical trial, the registry lists each of the specific patient groups eligible to enroll in the trial—thus allowing a link between our measures of expected commercialization lag (survival time) and R&D activity (clinical trial investments) across cancer types and stages of disease.

Using this data, we document that, consistent with our conjectured distortion, patient groups with longer commercialization lags (as proxied by higher survival rates) tend to have lower levels of R&D investment. Panel A of Figure 1 gives a sense of this basic pattern using stage-level data. On average, metastatic cancer patients have a five-year survival rate of approximately 10 percent, and have nearly 12,000 clinical trials in our data. In contrast, localized cancer patients have a five-year survival rate of approximately 70 percent, and have just over 6,000 clinical trials in our data. This pattern is even more stark if we contrast recurrent cancers (advanced cancers with very poor survival prospects) and cancer prevention: fewer than 500 trials in our data aim to prevent cancer, whereas recurrent cancers have more than 17,000 trials. A rough adjustment for market size—looking at the number of clinical trials per life-year lost from cancer—does little to change this basic pattern.

This new fact—a negative correlation between commercialization lags and R&D investments—is consistent with our conjectured distortion. However, by itself this fact is difficult to interpret for two reasons. First, this correlation need not reflect a causal relationship between commercialization lags and R&D investments. For example, if scientific opportunities are comparatively scarce for early-stage cancers, then a policy that shortened commercialization lags may have no effect on R&D investments. Second, even if this fact did reflect a causal effect of commercialization lags on R&D investments, on its own this fact need not be evidence of a distortion. As clarified by our theoretical model, the social planner is also more likely to pursue

research projects that can be completed more quickly. To address these two concerns, we document evidence from two complementary empirical tests.

First, we document causal evidence that shortening commercialization lags increases R&D investments. The key idea behind this test is to take advantage of the fact that some types of cancers are allowed to use surrogate endpoints (that is, non-mortality based clinical trial endpoints), which break the link between patient survival rates and clinical trial length. We document that there is *not* a negative relationship between survival time and R&D in the sample of cancers allowed to use surrogate endpoints. This suggests that our cross-sectional fact is unlikely to be explained by factors such as the pattern of available scientific opportunities. However, this test leaves open the possibility that the social planner and private firms symmetrically respond to commercialization lags, and thus does not provide direct evidence of a distortion.

Second, we contrast public and private R&D investments. Consistent with our model, we document that commercialization lags reduce both public and private R&D investments. But also consistent with our model—and consistent with the conjectured distortion—we document that the commercialization lag-R&D correlation is quantitatively and statistically significantly more negative for privately financed trials than for publicly financed trials.

As a complement to these empirical analyses, we also provide case study evidence documenting that all six FDA-approved cancer prevention technologies—technologies that should have long commercialization lags, and hence should be affected by the conjectured distortion—either relied on the use of surrogate endpoints or were approved on the basis of publicly financed clinical trials. That is, with the exception of a few instances where surrogate endpoints were able to be utilized, there have been zero privately developed chemoprevention drugs. Taken together, this body of evidence provides support for the idea that commercialization lags distort private R&D investments.

Our theoretical model describes two potential mechanisms for our empirical results—corporate short-termism and the patent distortion—but our results do not speak to which mechanism is quantitatively more important. The existing literature also provides little insight into the expected magnitudes of either mechanism. On one hand, the corporate finance literature has struggled to devise tests for the presence of short-termism bias, in part because the key theoretical implications often focus on behaviors that by construction are undertaken by managers but unobserved by the market. Perhaps most closely related is Bernstein (forthcoming), who documents that public firms pursue lower "quality" R&D than privately held firms, but he lacks a direct measure of commercialization lags. On the other hand, the innovation literature has provided remarkably little evidence that stronger patent protection induces more R&D investments. For example, Lerner (2002) and Sakakibara and Branstetter (2001) find little evidence that stronger intellectual property rights induce more R&D.[6]

[6] While the prior innovation literature has primarily focused on how patents affect the level of R&D, note that our model suggests a mechanism through which the structure of the patent system may also have important effects on the direction of R&D. This idea has been discussed by several legal scholars (Eisenberg 2005; Abramowicz 2007; Roin 2010), but to the best of our knowledge has not previously been formally investigated either theoretically or empirically.

We use our theoretical model to analyze the innovation and social welfare consequences of three policy levers that could address this distortion: allowing firms to rely on surrogate endpoints in clinical trials, a patent design change that would start the patent clock at commercialization, and R&D subsidies targeting projects with long commercialization lags. Two aspects of this analysis are important to highlight. First, surrogate endpoints have benefits beyond just eliminating the distortion, because the social planner also values completing projects more quickly. Second, patent reforms would address only the distortion generated by patents, and would not address the distortion generated by corporate short-termism. Given that our empirical work does not quantify the relative importance of corporate short-termism and patents, our analysis of patent reforms as a policy lever should be considered suggestive rather than conclusive.

Our empirical focus on cancer treatments is of substantive interest because of cancer's tremendous morbidity and mortality burden. In 2009, cancer was the second leading cause of death in the United States (after heart disease), accounting for almost 25 percent of all deaths. Using an economic framework which values improvements in health based on individuals' willingness to pay, Murphy and Topel (2006) estimate that a permanent 1 percent reduction in cancer mortality has a present value to current and future generations of Americans of nearly $500 billion, and that a cure (if feasible) would be worth about $50 trillion. Taking advantage of our surrogate endpoint variation, we estimate counterfactual R&D allocations and induced improvements in cancer survival rates that would have been observed if commercialization lags were reduced. Based on these counterfactuals, we estimate that among one cohort of patients—US cancer patients diagnosed in 2003—longer commercialization lags generated around 890,000 lost life-years; valued at $100,000 per life-year lost (Cutler 2004), the estimated value of these lost life-years is on the order of $89 billion.

The paper proceeds as follows. Section I presents the model. Section II describes our data. Section III documents the negative correlation between survival time and R&D investments, and Section IV interprets this relationship. Section V derives a back-of-the-envelope estimate of the life-years lost due to longer commercialization lags. Section VI concludes.

I. Theory

We conceptualize R&D as consisting of two stages: invention and commercialization. By invention we mean developing the basic idea for a product to the point where it is patentable: producing a new chemical compound, building a prototype, etc. By commercialization we mean all that is involved in bringing an invented product to market: getting FDA approval for the new chemical compound, producing the prototyped good at efficient scale, etc. The commercialization lag of an R&D project is the amount of time between invention and commercialization.

Our purposefully simple model shows why private-sector R&D may be distorted away from inventions with long commercialization lags. Note importantly that both private and social R&D incentives decline with commercialization lag—all else equal, both firms and society prefer inventions to come to market quickly. But, due to either excessive discounting or the fixed patent term, private incentives will

decline more rapidly than social incentives, which is what gives rise to the distortion. Our model also analyzes three potential policy interventions which can be used to address this distortion.

Reflecting our empirical setting we focus the model on the pharmaceutical industry, though our analysis applies more broadly.

A. *Preliminaries*

A representative firm conducts undirected R&D which stochastically yields inventions. Whenever the firm's undirected R&D yields an invention, it then must decide whether to invest directed R&D toward the goal of commercializing the specific invention. An invention is characterized by the following parameters:

Timing Parameters.—The year in which the invention is realized by the firm's undirected R&D is t_{invent}, which we normalize to zero. The number of years that the commercialization effort will take is t_{comm}, which we call *commercialization lag*. In the context of the pharmaceutical industry, commercialization lags arise both in research and in clinical development; to fix ideas, think of t_{comm} as the number of years that it will take to conduct US Food and Drug Administration (FDA)-required clinical trials. We treat t_{comm} and several other parameters below as deterministic for simplicity; in practice many of the parameters would be stochastic.

Cost of Commercialization.—If the firm elects to commercialize the invention it incurs commercialization costs of c. For simplicity, we treat commercialization costs as a one-time cost incurred at time t_{invent}.[7] Conceptually, we think of the firm as deciding at time t_{invent} whether to allocate capital to the project, e.g., in pharmaceuticals, the firm decides at time t_{invent} whether to invest in conducting clinical trials.

Likelihood of Successful Commercialization.—The commercialization effort yields a commercially viable product with probability p. The success parameter p can be interpreted as the likelihood that FDA clinical trials are successful.

Obsolescence Risk.—If the product is successfully commercialized, then it is useful until superseded. We model obsolescence risk in a simple way, assuming that obsolescence occurs with probability $1 - \gamma$ per year in each year following t_{invent}.[8] Obsolescence risk would more appropriately be modeled as an endogenous parameter (for example, a function of R&D investments); for simplicity we follow much of

[7] An alternative approach would be to interpret c as the net present value of costs that are incurred over t_{comm} years, but this raises the issue of which discount factor to use for the purpose of computing this net present value—the neoclassical discount factor δ or the short-termism discount factor $\eta\delta$. Treating costs as incurred at time t_{invent} circumvents this issue, and captures the idea that clinical trials require similar financial resources whether they are funded by a private firm or the government. Our approach also abstracts from staged investment and the associated real-option considerations which, while important, are not directly related to the goals of our model: see, e.g., Gompers (1995) and Neher (1999) for analyses of staged financing.

[8] An alternative would be to incorporate obsolescence that occurs before t_{comm} into the probability of commercialization success p, and only use the term obsolescence to describe cases where the product is superseded after successful commercialization at t_{comm}. This is economically equivalent, but less convenient mathematically; see especially formula (1) below.

the previous patent theory literature in taking obsolescence risk as exogenous (e.g., Grossman and Lai 2004).[9]

Monopoly Profits and Social Value.—If the product is successfully commercialized, non-obsolete, and protected by patent, it yields profits of π per year to the inventing firm, and social value of v^{monop} per year.[10] If the product were priced by a social planner instead of a monopolist, it would yield social value of $v > v^{monop}$ per year.

Imitability.—If the product is successfully commercialized, non-obsolete, and not protected by patent, generic entrants may imitate the commercialized product.[11] Imitation reduces the inventing firm's profits from π to $(1 - \iota)\pi$, where $\iota \in [0, 1]$ denotes the imitability of the product (that is, vulnerability to generic competition). The case $\iota = 1$ corresponds to perfect imitability, which drives the inventing firm's profits to zero. We focus on $\iota = 1$ for most of the analysis, but note that even in pharmaceuticals generic entry sometimes does not drive profits all the way to zero (see Bronnenberg et al. 2013).

Discounting and Excess Impatience.—The project's neoclassical risk-adjusted discount rate is r. Following Stein (2003), corporate short-termism can be modeled as an excessive private-sector discount rate. For mathematical convenience we work with discount factors instead of discount rates, so corporate short-termism is reflected as a lower discount factor. Specifically, society applies the obsolescence-risk-weighted discount factor $\delta = \gamma/(1 + r)$, whereas private firms apply the discount factor $\eta\delta$, with $\eta \leq 1$. The η term reflects excess impatience due to corporate short-termism.

Patent Term and Timing of Patent Filing.—In a fixed-term patent system, patents for new inventions last t_{patent} years from the filing date.[12] So long as an invention is protected by patent, imitation is illegal. Firms may choose whether to file for patent protection at the time of invention t_{invent} or at the time of commercialization t_{comm}. If they file at the time of invention they receive patent protection with probability 1. If they wait until commercialization to file they receive patent protection with probability $q \leq 1$, reflecting the risk of disclosure, losing an R&D race, etc. Pharmaceutical firms face very strong incentives to file patents at the time of invention (Wegner and Maebius 2001; Galli and Faller 2003; Schreiner and Doody 2006):

[9] Across industries, many inventions become obsolete long before their patents expire (Schankerman and Pakes 1986). However, this is generally not the case in the pharmaceutical industry, as many drugs are still in use long after their initial FDA approval date and generate significant sales revenues near the end of their patent term (Grabowski and Kyle 2007).

[10] A natural alternative assumption would be to model profits as endogenous to entry, since more competition could result in lower profits. We do not focus on this possibility here given that in our context, this would cut against our distortion: projects with short commercialization lags should have more entry, and be lower profit, which would in turn lower incentives for subsequent entry. Given that our data suggest that this dynamic is not sufficiently strong to offset our main finding—that projects with short commercialization lags have more entry—we focus on an exogenous profit parameter for simplicity.

[11] In the pharmaceutical industry, generic manufacturers are usually poised to enter the market as soon as patents expire (Grabowski and Kyle 2007; Hemphill and Sampat 2012). Such formal analyses are consistent with anecdotal evidence that industry analysts, and, e.g., the *Wall Street Journal,* closely track patent expirations in the pharmaceutical industry, and these patent expirations tend to result in sharp changes in the profitability of branded drugs.

[12] We here abstract away from the provisions of the 1984 Hatch-Waxman Act, which awards some qualifying pharmaceutical firms extended patent terms; we discuss such policy levers in Section IE.

delaying risks a competitor patenting first, or subsequent disclosures undermining the drug's novelty or non-obviousness for purposes of patentability (Thomas 2007; Patrick 2005; Zanders 2011).[13] In practice, firms almost always have possession of the core patents over their drugs before entering clinical trials (Mossinghoff 1999; Patrick 2005; Thomas 2007).[14] For this reason we focus on the case of $q = 0$ for most of the analysis.

B. *Effective Monopoly Life and Effective Total Life*

We define an invention's *Effective Monopoly Life* (*EML*) as the expected number of years, in present value terms as discounted by the private firm, that the firm can expect to earn monopoly profits from the commercialized product. This is the expected amount of time that the invention is commercially viable, protected by patent, and not yet superseded. We focus our analysis on the case of inventions that are imitable if not protected by patent ($\iota = 1$) and where firms must file for patent protection at invention in order to receive patent protection ($q = 0$). This is the most relevant case for the pharmaceutical industry; below we discuss other cases.

If $t_{patent} > t_{comm}$ then EML can be written as

$$EML = p \sum_{t_{comm}}^{t_{patent}-1} (\eta\delta)^t = p \frac{(\eta\delta)^{t_{comm}} - (\eta\delta)^{t_{patent}}}{1 - \eta\delta}. \tag{1}$$

The key thing to notice about equation (1) is the role of the timing parameters: at best, the period of monopoly is from t_{comm} to t_{patent}. This best case occurs if the invention is successfully commercialized (which occurs with probability p) and not superseded as of time t_{patent} (obsolescence risk is incorporated into δ). As soon as time reaches t_{patent}, the invention will be imitated and the monopoly position lost. Note as well that if $t_{patent} \leq t_{comm}$, then $EML = 0$: by the time the invention is commercialized, patent protection has expired.

Next, we define an invention's *Effective Total Life* (*ETL*) as the expected number of years, in present value terms as discounted by society, that the invention will be commercialized and non-obsolete,

$$ETL = p \sum_{t_{comm}}^{\infty} \delta^t = p \frac{\delta^{t_{comm}}}{1 - \delta}. \tag{2}$$

There are two differences between *EML* and *ETL*. First, monopoly life runs at best until t_{patent}, whereas total life runs indefinitely until the invention becomes obsolete.

[13] Zanders (2011, pp. 322–23), for example, argues: "A question that is often raised during my courses is 'why don't companies wait as long as possible before patenting?' This is tempting, but given the fluid nature of employment in the industry and the general leakiness of information, this would be tantamount to commercial suicide."

[14] Although the law is not settled, FDA clinical trials most likely constitute a public disclosure of the drug; see *SmithKline Beecham Corp. v. Apotex Corp.,* 365 F.3d 1306, 1318 (Fed. Cir. 2004), *opinion vacated and superseded*, 403 F.3d 1331 (Fed. Cir. 2005). The SmithKline decision held that a drug's use in clinical trials puts it in the public domain, but since that opinion was vacated and the court decided the case on other grounds, the state of the law here is unclear. Once an invention is in the public domain, the inventing firm must file for patent protection within one year of public disclosure else they lose the right to patent (35 USC. 102).

Second, monopoly life is measured according to the private-sector discount factor $\eta\delta$ whereas total life is measured according to the social discount factor δ.

If the invention is not perfectly imitable ($\iota < 1$) then the formula for *EML* would need to be modified to account for the fact that profits do not fall all the way to zero at t_{patent}.[15] In the extreme case of zero imitability ($\iota = 0$) and zero short-termism ($\eta = 1$), *EML* and *ETL* coincide. If the invention has q that is not only strictly positive but sufficiently large, then the formula for *EML* would need to be modified to account for the fact that firms may choose to file for patent protection at t_{comm} rather than t_{invent}.[16] In this case, the period of monopoly protection runs from t_{comm} to $t_{comm} + t_{patent}$, but the firm enjoys a successful, patent-protected invention with probability of just pq rather than p.

C. *Private and Social Incentives to Invest*

A profit-maximizing firm attempts to commercialize an invention if and only if the expected profits exceed the costs,

$$\text{Private Investment Occurs} \Leftrightarrow EML \cdot \pi \geq c. \tag{3}$$

In words, the firm can expect to enjoy monopoly profits of π for *EML* years. If $EML \cdot \pi$ exceeds the costs of commercialization c, it is optimal to commercialize.

Suppose instead that society owned the firm. If commercialization is successful, the social planner will price at marginal cost, and hence create social welfare of v per year. Hence the social planner attempts to commercialize the invention if and only if expected social welfare, if the good is priced at marginal cost, exceeds the costs of commercialization,

$$\text{Investment is Socially Optimal} \Leftrightarrow ETL \cdot v \geq c. \tag{4}$$

Notice that $ETL \geq EML$ and $v \geq \pi$ by definition. By construction, this ignores issues such as business stealing and R&D races which, although important, are not the focus of our analysis.[17] Thus, in our framework, anytime a private firm would choose to commercialize an invention, so too would the social planner. The projects that the private firm does not pursue, but that society would pursue if it owned the firm, are those where

$$\text{Private and Social Investment Differ} \Leftrightarrow \frac{EML \cdot \pi}{c} \leq 1 \leq \frac{ETL \cdot v}{c}. \tag{5}$$

In words, private and social investment decisions differ when the social return is positive but the private return is negative. The private market can under-provide R&D if either $EML/ETL < 1$ or $\pi/v < 1$.

[15] The modified formula becomes $EML = p\left(\sum_{t_{comm}}^{t_{patent}-1}(\eta\delta)^t + (1-\iota)\sum_{t_{patent}}^{\infty}(\eta\delta)^t\right)$.

[16] The specific condition to check to see whether firms prefer to patent at t_{invent} or t_{comm} is which is larger of $p\sum_{t_{comm}}^{t_{patent}-1}(\eta\delta)^t$ or $pq\sum_{t_{comm}}^{t_{comm}+t_{patent}-1}(\eta\delta)^t$. Clearly, the former is larger for sufficiently small q (as is the case in pharmaceuticals) and the latter is larger for sufficiently large q.

[17] Bloom, Schankerman, and Van Reenen (2013) provide a recent analysis estimating the magnitude of business stealing.

D. *Distortions in the Level and Composition of R&D*

Our model yields distortions, relative to the social optimum, in both the level and composition of commercialization activity. By distortion in level, we mean simply that fewer inventions are commercialized by private firms than would be the case if the social planner made commercialization decisions. This is a standard result. By distortion in composition, we mean that the private market may choose to commercialize A but not B, while a social planner would prefer to commercialize B over A. That is, the private sector not only pursues too little R&D relative to the social optimum, but also chooses the wrong projects relative to what the social planner would choose. We state this formally as follows:[18]

PROPOSITION 1: *The private firm's commercialization activity differs from the social optimum in both the level and the composition:*

(*i*) (*Distortion in levels*) *Commercialization activity is strictly lower than socially optimal, unless* (*i*) *patent terms are infinite* (*i.e.,* $t_{patent} = \infty$); (*ii*) *firms are not excessively impatient* (i.e., $\eta = 1$); *and* (*iii*) *monopolists capture full social surplus* (i.e., $\pi = v$).

(*ii*) (*Distortion in composition*) *For two inventions, A and B, it is possible that the expected social return* ($ETL \cdot v/c$) *to pursuing invention A exceeds that of invention B, yet invention A is not pursued while invention B is. For this to be the case, at least one of the following must hold:*[19]

(*a*) $\pi_B/v_B > \pi_A/v_A$, *i.e., monopolists capture more profit as a proportion of potential social value from invention B than from invention A.*

(*b*) $EML_B/ETL_B > EML_A/ETL_A$, *i.e., the ratio of monopoly life to total useful life is larger for invention B than for invention A.*

As noted above, Part 1 of Proposition 1 is a standard result, which indicates that the private sector pursues too little inventive activity relative to the first best. Part 2 of Proposition 1 indicates that distortions in composition can arise from differences across inventions in either π/v or EML/ETL.

An invention's profitability to social value ratio π/v depends on the monopolist's ability to capture the value its invention creates.[20] One extreme case is if the monopolist can perfectly price discriminate, in which case $\pi/v = 1$. The other extreme case is inventions that are non-excludable, in which case $\pi/v = 0$. An example of the latter is a study on a non-excludable form of disease

[18] Proofs are presented in online Appendix A.

[19] We use subscripts *A* and *B* to denote the project-specific parameters associated with these specific inventions (e.g., π_A is the monopoly profits associated with successful commercialization of invention *A*).

[20] Past authors have estimated that on the whole, pharmaceutical firms appropriate only a small share of the social value of their innovations—generally between 2–20 percent (Philipson and Jena 2006; Lakdawalla et al. 2010; Lindgren and Jonsson 2012). Nordhaus (2004) estimates that this general conclusion holds outside of the pharmaceutical industry as well, arguing that only a minuscule fraction of the social returns from technological advances over the 1948–2001 period was captured by producers.

prevention: e.g., a profit-maximizing firm would never conduct an expensive clinical trial to test whether a particular pattern of cardiovascular exercise reduces the risk of heart disease, because knowledge that a specific pattern of exercise reduces the risk of heart disease is non-excludable.

An invention's monopoly-life to total-life ratio, EML/ETL, describes the proportion of the invention's total useful life in which the private firm enjoys monopoly profits. Our central point is that an invention's EML/ETL ratio declines with commercialization lag t_{comm}, due to both short-termism and the fixed patent term. To see this, write out the expression for EML/ETL assuming that $t_{comm} \leq t_{patent}$:

$$\frac{EML}{ETL} = \frac{p\frac{(\eta\delta)^{t_{comm}} - (\eta\delta)^{t_{patent}}}{1-\eta\delta}}{p\frac{\delta^{t_{comm}}}{1-\delta}} = \frac{1-\delta}{1-\eta\delta}\left(\eta^{t_{comm}} - \eta^{t_{patent}}\delta^{t_{patent}-t_{comm}}\right). \tag{6}$$

Notice, first, that if $\eta = 1$ and $t_{patent} = \infty$ (there is no short-termism and patent length is infinite), then $EML/ETL = 1$ for all t_{comm}.[21] Commercialization lag reduces incentives to invest, but it reduces both private and social incentives to invest at exactly the same rate.

Notice, too, that if $\eta = 1$ and $t_{patent} = t_{comm} + k$, that is, the patent term is finite but with the patent clock modified to start at commercialization, not invention (recall that we have normalized $t_{invent} = 0$), then EML/ETL again doesn't vary with t_{comm}. EML is strictly less than ETL under this patent design, but, just as with infinite patents, commercialization lag reduces private and social incentives at exactly the same rate.

However, if either $\eta < 1$ or the patent term is finite and starts at invention, then EML/ETL declines with t_{comm}. The decline in private incentives is more rapid than the decline in social incentives.

PROPOSITION 2: *Comparative statics of an invention's proportion of monopoly life to total life, EML/ETL, on its commercialization lag, t_{comm}:*

(*i*) *If there is no short-termism ($\eta = 1$) and the patent term is either infinite ($t_{patent} = \infty$) or is finite but the clock starts at commercialization ($t_{patent} = t_{comm} + k$ for finite k), then the ratio of monopoly life to total life, EML/ETL, is constant in t_{comm}: $\partial(EML/ETL)/\partial t_{comm} = 0$.*

(*ii*) *If firms are excessively impatient ($\eta < 1$) or the patent term is finite and starts at invention, EML/ETL is decreasing in t_{comm}.*

(*a*) *If $t_{comm} < t_{patent}$ the decline is strict: $\partial(EML/ETL)/\partial t_{comm} < 0$.*

(*b*) *If $t_{comm} \geq t_{patent}$ then $EML = 0$. Hence $EML/ETL = 0$.*

[21] Recall that while our analysis focuses on the case of perfect imitability ($\iota = 1$), an economically equivalent condition to $t_{patent} = \infty$ is if $\iota = 0$. We discuss imperfect imitability in Section IE.

This result, in combination with Proposition 1, shows that private-sector R&D is particularly distorted away from R&D projects with long commercialization lags, relative to projects with shorter commercialization lags. Moreover, there is a sense in which the effect of excess impatience on $\partial(EML/ETL)/\partial t_{comm}$ and the effect of the fixed patent term on $\partial(EML/ETL)/\partial t_{comm}$ reinforce each other. The fixed patent term means that increasing t_{comm} by one year reduces the number of calendar years of monopoly life by one year. Excess discounting means that the private firm places too little weight on each of these years of monopoly life relative to their societal value. To see this decomposition formally, define an invention's *effective patent life* as $EPL = p\sum_{t_{comm}}^{t_{patent}-1}\delta^t = p(\delta^{t_{comm}} - \delta^{t_{patent}})/(1-\delta)$; EPL is EML but using the social discount factor δ. We can decompose EML/ETL into an excessive discounting term and a fixed patent term as

$$\frac{EML}{ETL} = \underbrace{\frac{EML}{EPL}}_{\text{excess discounting}} \cdot \underbrace{\frac{EPL}{ETL}}_{\text{fixed patents}}. \tag{7}$$

It is easy to see that both terms in this decomposition are strictly declining with commercialization lag:

PROPOSITION 3: *Decomposition of $\partial(EML/ETL)/\partial t_{comm}$ into the effect of excess discounting and the effect of the fixed patent term:*

(*i*) *If there is excess discounting, $\eta < 1$, then $\partial(EML/EPL)/\partial t_{comm} < 0$ for $t_{comm} < t_{patent}$.*

(*ii*) *If there is a fixed patent term—a finite patent clock that starts at invention—then $\partial(EPL/ETL)/\partial t_{comm} < 0$ for $t_{comm} < t_{patent}$.*

Two hypothetical examples can illustrate this distortion in the composition of R&D. A vaccine administered to men at age 20 which prevented prostate cancer (which tends to affect men in their fifties or later) would have a high social value v (given the high morbidity and mortality burden of prostate cancer), but would have a low (or zero) EML/ETL ratio because of the long required clinical trials. In contrast, a drug administered to late-stage prostate cancer patients which extended life from, say, six months to eight months, would have a lower social value v, but a high EML/ETL ratio because of the short required clinical trials. Note that in the case of these examples, our distortion of interest—generated by the difference in EML/ETL ratios—would be reinforced by differences in π/v.

E. *Policy Responses*

Our empirical work will provide support for the idea that private-sector R&D activity is distorted away from projects with long commercialization lags. Given that evidence, in this subsection we discuss the innovation and social welfare consequences of three policy interventions that could be used to address this distortion: a policy change that would allow firms to rely on surrogate (non-mortality) endpoints in clinical trials; a patent design change that would start the patent clock at

commercialization; and targeted R&D subsidies. Some readers may prefer to skip this section on a first reading, returning to our analysis of policy responses after reading the empirical analysis.

Policy Lever: Surrogate Endpoints.—A major factor determining the duration of a clinical trial is the amount of time needed to observe statistically significant differences in treatment outcomes among enrolled patients, known as the "follow-up period." The length of the follow-up period largely depends on two factors: the natural progression of the disease, and the clinical trial endpoints required by government regulators.

Prior to marketing a new drug, firms must submit clinical trial results to the US Food and Drug Administration (FDA) documenting that their product meets a set of safety and efficacy standards. Over time, the FDA's interpretation of which clinical trial endpoints can be used to support claims that a drug is effective have varied (see, e.g., Johnson, Williams, and Pazdur 2003). Conventionally, clinical trials evaluate whether a candidate product provides a clinical benefit to mortality—be it overall survival or a closely related measure such as "disease free survival," which measures time until cancer recurrence. However, in recent years there has been increased interest in using surrogate endpoints as a substitute for the standard clinical endpoints in a drug trial. In the case of hypertension, for example, lower blood pressure is accepted as a surrogate for the clinical endpoint of preventing cardiovascular complications (Lee et al. 2006). As we discuss in Section IVA, blood cell counts and related measures have been accepted surrogate endpoints for hematologic malignancies (leukemias and lymphomas).

Surrogate endpoints have the potential to dramatically reduce the length of clinical trials necessary to test whether a drug is effective. However, surrogate endpoints have also been extremely controversial. As described by Fleming (2005), although treatment effects on surrogate endpoints clearly establish some form of biological activity, changes in surrogate endpoints may not correlate with changes in the clinical endpoint of interest. As an example, he discusses prostate specific antigen (PSA) levels: although PSA levels are correlated with the extent of prostate cancer, the PSA level itself is not a mechanism through which prostate cancer progresses, and thus it is unknown whether a treatment that reduced PSA levels in prostate cancer patients would generate improvements in survival.[22] Reflecting this type of concern, most cancers use surrogate endpoints only on a limited, somewhat ad hoc basis.[23]

[22] A non-cancer example of the controversy around surrogate endpoints arose recently in the context of treatments for early-stage Alzheimer's disease. In a 2013 editorial in the *New England Journal of Medicine*, two FDA officials discussed the possibility of accepting new types of surrogate endpoints in clinical trials of treatments for early-stage Alzheimer's disease (Kozauer and Katz 2013)—a proposal that was sharply criticized by the editorial board of the *New York Times* ("Drugs for Early-Stage Alzheimer's," March 18, 2013), among others.

[23] As discussed by US Food and Drug Administration (2007) and Johnson, Williams, and Pazdur (2003), since 1992 the FDA's accelerated approval regulations have allowed for the following: for diseases that are serious or life-threatening, a drug can be FDA approved based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not established at a level that would support regular approval, under the condition that the applicant is required to perform a post-marketing study to demonstrate that treatment with the drug is indeed supported with clinical benefit. If the subsequent trials fail to demonstrate clinical benefit, or if the applicant does not conduct the required studies, the FDA can act quickly to remove the drug from the market. A recent President's Council of Advisors on Science and Technology (2012) report argued that the FDA should expand this accelerated approval program.

In the context of our model, surrogate endpoints can be conceptualized as strictly reducing commercialization lag t_{comm}: firms can always choose to use survival as an endpoint, and we assume that the surrogate endpoint can be observed strictly earlier than the survival outcome. For simplicity, we analyze the effect of an "ideal" surrogate endpoint—one that perfectly correlates with the true clinical outcome of interest. This assumption allows us to make the following simple point.

PROPOSITION 4: *Allowing surrogate endpoints:*

(*i*) *Strictly increases commercialization activity: some inventions that would not otherwise have been commercialized now are, and all inventions that would be commercialized even without surrogate endpoints still are.*

(*ii*) *Strictly increases firm profits and social welfare.*

(*iii*) *Let* $\hat{t}_{comm}$ *denote commercialization lag, in the absence of a surrogate endpoint, based on the time required to show an effect on patient mortality. Let* $t_{comm} < \hat{t}_{comm}$ *denote the commercialization lag if surrogate endpoints are allowed. If* t_{comm} *is independent of* $\hat{t}_{comm}$*, that is, if the time required to show impacts on the surrogate endpoint is independent of the time required to show impacts on mortality, then allowing surrogate endpoints eliminates the distortion in composition associated with commercialization lag absent the surrogate endpoint:* $\partial E\left(\frac{EML}{ETL} | \hat{t}_{comm} = x\right)/\partial x = 0$.

Clearly this proposition is based on a strong assumption of the existence of an ideal surrogate endpoint. Our objective here is simply to show that there would be social welfare benefits from the scientific discovery, validation, and allowance of valid surrogate endpoints.[24] Note that surrogate endpoints are valuable both because they eliminate the distortion in composition of R&D and because, even in the absence of a distortion, it is socially valuable to complete R&D projects sooner.

Patent Design.—In this section we discuss modifications to the fixed term patent design that address the distortion away from long-term R&D projects. Note, importantly, that the patent design policy response differs from our other policy responses in that it addresses only the fixed patent term as a source of distortion, and not excessive discounting. As we will discuss below, if patents are unimportant for motivating R&D (formally, imitability ι is zero), the patent design policy response will not be effective at addressing the distortion of interest, but in our simple framework this policy reform would also not be harmful.[25]

[24] The use of invalid surrogate endpoints could increase R&D investments but not generate any corresponding gains in survival. In the specific empirical context we analyze in Section IVA, we will document evidence that surrogate endpoints for hematologic cancers appear to have increased R&D investments, and that this increase in R&D investments appears to have translated into real improvements in patient health.

[25] Our model focuses on a Nordhaus (1969)-style trade-off between the incentives for developing a new innovation and the deadweight loss of higher prices during the life of the patent. By construction, this type of framework abstracts away from other ways in which patent reforms could impact social welfare, including business stealing, the effects of patents on follow-on innovation, litigation, or the benefits of the disclosure function of the patent system.

We begin with a simple result, analogous to part (i) of Proposition 2, that shows that starting the patent clock at commercialization, rather than invention, eliminates the distortion in composition arising from the patent system.

PROPOSITION 5: *If the patent clock starts at commercialization, i.e.,* $t_{patent} = t_{comm} + x$ *for fixed and finite* x*, then EPL/ETL is independent of commercialization lag,* t_{comm}*.*

If we make some admittedly stylized assumptions on the distribution of invention possibilities, we can make a stronger claim, which is that starting the patent clock at commercialization strictly increases social welfare. In fact, the result says we should go further: social welfare is maximized by awarding *more* post-commercialization patent life to inventions with longer commercialization lag than inventions with shorter commercialization lag, in contrast to the current system which awards inventions with longer commercialization lag *less* post-commercialization patent life than inventions with shorter lag.

PROPOSITION 6: *Make the following assumptions about the distribution of invention parameters:* $\delta < 1$ *and* $\eta \leq 1$ *are constant across inventions, so that EML varies only with commercialization lag* t_{comm}*, patent life* t_{patent}*, and success probability* p*; the social-to-private value ratios* v/π *and* v^{monop}/π *are constant across inventions; the density of inventions on the extensive margin, i.e., the expected number of new inventions elicited by a marginal increase in* t_{patent}*, is uniform; and, the expectation of costs,* c*, conditional on an invention being at the margin, is weakly increasing in* t_{comm}*. Suppose that private firms make commercialization decisions according to equation* (3)*. Suppose that the length of the patent award can be conditioned on* t_{comm} *but not on the other invention parameters. Then socially optimal patent policy requires that the number of years of post-commercialization patent protection increases monotonically with* t_{comm}*, whereas under the fixed-term patent system the number of years of post-commercialization patent protection decreases monotonically with* t_{comm}*.*

The intuition for this result, which was conjectured informally in Roin (2010), is as follows. Fix a level of t_{comm}, and consider an increase in post-commercialization patent life for inventions with this commercialization lag. This increase in patent protection has benefits and costs. The benefit is that more inventions with commercialization lag t_{comm} will be commercialized at the margin; technically, we have increased *EML* and hence made it more likely that equation (3) obtains. The cost is that, for inframarginal inventions that would have been pursued absent the increase in patent protection, there is more deadweight loss, for the standard reason that social value under monopoly is smaller than social value under perfect competition from generic entrants. The proof makes two key observations. First, the deadweight loss costs on the intensive margin are strictly decreasing with t_{comm}, both because the costs are pushed out further into the future and because the set of invention parameters for which private firms choose to commercialize is shrinking. Second, the benefits at the extensive margin are actually increasing with t_{comm}: for a private firm to be willing to commercialize an invention with higher t_{comm}, the invention

must be higher quality in the sense of higher private value π—especially if the firm is excessively impatient—which in turn implies higher social value v^{monop} and v.[26] Intuitively, when t_{comm} is large, the inventions at the margin are especially worth encouraging, and the cost of doing so is comparatively low. Hence, the larger is t_{comm}, the larger should be post-commercialization patent life.

We wish to make four further remarks concerning this result. First, conditioning the length of patent award on t_{comm} should be feasible in practice, at least in the case of pharmaceuticals, since completion of FDA trials is intrinsically an observable event. Second, while we acknowledge that our assumption of constant social-to-private value ratios v^{monop}/π and v/π is stylized, we note that the types of inventions that take longer to reach the market (e.g., treatments of early-stage disease and disease prevention) seem likely to have especially high such ratios. If these ratios increase with t_{comm}, then this increases the rate at which benefits at the extensive margin increase with t_{comm}, strengthening the result. Third, the 1984 Hatch-Waxman Act[27] contains a provision granting some qualifying firms a partial extension of patent life based on the time that the drug spent in clinical trials. Specifically, the act awards qualifying firms an additional half-year of patent life for every year spent in clinical trials, up to a maximum of 5 years not exceeding 14 total years. Our result says that the Hatch-Waxman extension is directionally correct, but that optimal policy would go further. Finally, we are here abstracting away from strategic responses that could be "unintended consequences" from such a change in patent policy.[28] In practice, awarding FDA-granted exclusivity periods that run from the date of FDA approval would likely accomplish the same goal, be administratively simpler to implement, and avoid unintended problems that could arise with revising the patent system.[29]

Our next result considers a more limited set of patent-design instruments than is allowed for by Proposition 6 and shows that there is still scope for improvement.

PROPOSITION 7: *Suppose that the length of the patent term must be fixed, but that the patent clock can start either at invention or commercialization. Make the same assumptions regarding the distribution of invention parameters as in Proposition* 6. *Given any patent term that runs from the date of invention, there exists a patent term that runs from the date of commercialization that strictly increases social welfare. In particular, the optimal patent term that runs from the date of commercialization is superior to the optimal patent term running from the date of invention.*

[26] It is not necessary for the result that benefits at the extensive margin are weakly increasing with t_{comm}, only that they do not decrease too quickly (i.e., faster than do the deadweight loss costs on the intensive margin). For this reason, several of the assumptions in the proposition can be slightly relaxed. We have a numerical example, in which the density of the extensive margin is bimodal with a large decline between the two modes, which illustrates that the conclusion of the proposition is false if the density falls off too quickly. Intuitively, in the region in which the density on the extensive margins is very low, it is not sufficiently socially valuable to elicit inventions on the extensive margin to justify the deadweight loss costs for inventions on the intensive margin.

[27] Public Law 98-417 (1984)

[28] More generally, we here restrict our attention to policy mechanisms that work within the existing patent system. More sophisticated policy mechanisms—for instance, in conjunction with the ideas in Kremer (1998) and Weyl and Tirole (2012)—could also be used.

[29] FDA exclusivity periods are currently granted to new drug applications (three years for new indications; five years for new molecular entities); to orphan drugs (seven years); and to pediatric approvals (six months).

Proposition 7 is useful for informing patent policy if it is possible to start the patent clock at commercialization, but difficult to condition the length of the patent award on the precise amount of time between invention and commercialization. As with the optimal policy considered above in Proposition 6, this more circumscribed policy proposal could be implemented via FDA-granted exclusivity periods as opposed to a restructuring of the patent system. A recent policy in the spirit of this result is a provision of the 2010 Patient Protection and Affordable Care Act,[30] which grants some qualifying drugs (specifically, biologic drugs) a 12-year exclusivity period running from the date of FDA approval, which runs concurrently with any remaining patent terms. Proposition 7 supports extending this type of post-approval exclusivity period to all drug approvals (but note that our analysis does not specify the optimal length of such an exclusivity period).

A caveat to the results in this section is that they presume that patents are an important way to incentivize research and development activity.[31] If patents do not increase research investments, the policy responses analyzed in this section would be ineffective. Formally, consider an industry in which imitability $\iota = 0$, so patents are not necessary to protect monopoly profits from projects. In such an industry, the modifications to patent design outlined in Propositions 5–7 will have no effect on R&D activity, although it is worth noting that in our simple framework these policy responses would not be harmful, only ineffective. By contrast, our other policy responses would be effective in such an industry provided that corporate short-termism is relevant ($\eta < 1$).

Policy Lever: Targeted R&D Subsidies.—The logic that targeted R&D subsidies can improve social welfare is simple and standard. Take a particular invention that is not pursued by the private sector, but that would be pursued in the first-best world, i.e.,

$$EML \cdot \pi < c < ETL \cdot v. \tag{8}$$

Suppose that the deadweight loss of taxation is τ per dollar spent. Then, so long as the magnitude of the potential social gain is large enough relative to the magnitude of the private loss—that is, the magnitude of the first inequality in (8) is small relative to the magnitude of the second inequality in (8)—there is a potential for welfare-increasing intervention.

Recall that we defined an invention's effective patent life as $EPL = p\sum_{t_{comm}}^{t_{patent}-1} \delta^t$, i.e., *EPL* is just like *EML* except that it uses the social discount factor δ rather than the private discount factor $\eta\delta$. The condition for the existence of a socially beneficial R&D subsidy is:

$$EML \cdot \pi < c \text{ and } c + \tau(c - EML \cdot \pi) < EPL \cdot v^{monop} + (ETL - EPL) \cdot v. \tag{9}$$

In words, the conditions are that, first, the private firm would not commercialize on its own, and, second, that the social value from commercialization exceeds the

[30] Public Law 111-148 (2010).

[31] As discussed in footnote 3, while patents have been controversial in many industries, a variety of sources of evidence suggest that patents are likely to be important in the pharmaceutical industry.

social costs—both the direct cost of commercializing, c, and the deadweight loss cost of the required subsidy. Notice that the private firm's commercialization decision (first without and then with the subsidy) depends on *EML*, whereas the value society gets from the commercialized invention during the period it is under patent protection depends on *EPL*.

While condition (9) can obtain for inventions with any commercialization lag, it is especially likely to obtain for inventions with large commercialization lags. This is because such inventions spend a larger proportion of their useful life off-patent, so it is more likely that on-patent life is not sufficient to incentivize private investment, while at the same time off-patent life is of sufficient importance that the value of public investment overcomes the deadweight loss of taxation. We can formalize this logic as follows.

PROPOSITION 8: *Make the same assumptions regarding the distribution of invention parameters as in Proposition* 6*. Suppose that private firms make commercialization decisions according to whether or not* $EML \cdot \pi + s \geq c$*, where* s *is an amount of government subsidy. Suppose that government R&D subsidies can be conditioned on* t_{comm} *but not on the other invention parameters. Then, for any target level of total subsidy expenditures, socially optimal subsidy policy requires that subsidies are strictly increasing in* t_{comm}*.*

The intuition for the proof of this result is similar to that for Proposition 6 on optimal patent length: the higher is t_{comm}, the higher is the quality of the marginally commercialized invention, and the smaller is the cost from needlessly subsidizing inframarginal inventions. As a policy matter, the most practical way to condition subsidies on t_{comm} might be to target subsidies at R&D that relates to treatment of early-stage disease and to disease prevention.

II. Data

Our empirical work focuses on cancer R&D for three reasons. First, unlike for many diseases, high-quality clinical data exists for cancer patients which accurately tracks patient-level characteristics such as survival time—a key variable needed for our analysis.[32] Second, the existence of a standardized classification system for cancer—namely, standardized cancer organs of origin (such as breast and lung) and stages of cancers at the time of diagnosis (such as localized and metastatic)—facilitates a relatively clean match between aggregated patient-level clinical data and information on clinical trial investments relevant to different groups of patients. Such a match is possible in large part because cancer drug development tends to be specific to the organ and stage of the primary tumor: for example, Genentech's drug Bevacizumab was approved by the FDA in 2004 for the treatment of patients

[32] The prostate cancer clinical trials discussed in the introduction illustrate why we would expect commercialization lags to be longer for clinical trials enrolling patients with longer expected survival times: because clinical trials must generally show evidence that treatments improve mortality-related outcomes, trials tend to be longer when enrolling patients with longer survival times. In online Appendix A, we outline a power calculation of the type used to guide the design of clinical trials in order to fix ideas on this point.

with metastatic carcinoma of the colon and rectum.[33] Cancer registry data records the organ and stage of the primary tumor at the time of diagnosis, thus allowing us to estimate the characteristics of patients (such as survival times) relevant to each cancer-stage. This mapping is of course imperfect: for example, the cancer registry data lacks the granularity required to precisely distinguish between hormone-receptor positive and hormone-receptor negative breast cancer patients. However, the level of clinical detail available in cancer registry data is remarkably complete relative to data available for other diseases. Finally, as discussed in the introduction, cancer is of interest from a substantive perspective given its high morbidity and mortality burden.

Sections IIA, IIB, and IIC describe our datasets, and Section IID presents some basic summary statistics. Online Appendix B describes our data construction in more detail.

A. *SEER Cancer Registry Data*

The clinical data we use is a standard patient-level research database called the Surveillance, Epidemiology, and End Results (SEER) data, compiled by the National Cancer Institute (NCI) and available for the years 1973–2009 (SEER 2012). SEER is considered the authoritative source of information on cancer incidence and survival in the United States. The key variables we use for our analysis are the following:

Cancer and Stage of Patients.—Physicians diagnose cancer by the organ of origin and by stages that correspond to the extent of the disease's spread at the time of initial diagnosis. We base our data construction on the standard SEER cancer classification system (including 80 cancer types) and the stage classification system that is most consistently available in the SEER data: localized, regional, and metastatic (listed in order of increasing extent of disease).[34] In addition to constructing cancer-stage-specific survival times, we also use information on the cancer and stage of diagnosis to construct a count of the number of patients diagnosed as a proxy for market size.

Survival Time.—SEER is administratively linked to follow-up mortality data from the National Center for Health Statistics (NCHS)—in our data, as of December 31, 2009. Our primary measure of survival time is five-year survival, defined over all uncensored patient cohorts (1973–2004). We also use an early cohort of patients

[33] This overly simplified description glosses over several important issues, including off-label use of cancer drugs, which we discuss more in online Appendix B.

[34] For more details, see the SEER training website: http://training.seer.cancer.gov/ss2k/staging/review.html. We exclude in situ cancers from our analysis given that this category is relevant for only a few cancers (breast, cervical, and melanoma), but our results are similar if these cancers are included. Two other cancer categories are important but not monitored in the patient-level cancer registry data: remission and recurrence. A cancer is said to recur if it returns after being undetectable for a period of time, and the time during which the cancer is undetectable is referred to as remission. In general, recurrence is associated with poor survival prospects, but given that the cancer registry data do not monitor remission or recurrence, it is not possible to empirically assign a survival time to these groups of patients. Reflecting this data limitation, we do not examine trials enrolling only remission or recurrence cases in our analysis. As shown in panel B of Figure 1, in situ and recurrent cancers fit our model well: with excellent (poor) survival prospects corresponding to few (many) clinical trials, respectively.

(1973–1983) with minimal censoring in our construction of the life lost measure described below.

Basic Patient Demographics at the Time of Diagnosis.—We use the year of diagnosis together with information on patient sex and age at diagnosis to merge on year-age-gender specific life expectancy data from the NCHS. We combine this data on average life expectancy (in the absence of cancer) with our measure of observed survival time for the 1973–1983 cohort in order to estimate the life lost due to cancer for each patient.

B. *National Cancer Institute Clinical Trials Registry*

To measure R&D investments in cancer treatments, we construct a new clinical trials dataset drawing on data from the US National Cancer Institute's Physician Data Query Cancer Clinical Trials Registry.[35] The NCI registry was established in 1971, and claims to be the most comprehensive cancer clinical trials registry. The intended purpose of the registry is to allow cancer patients and physicians to search for clinical trials currently accepting participants, and to allow them to access information and results from closed trials.

The NCI registry was not developed as a research database and—to the best of our knowledge—has not previously been used as a data source by other researchers. The key advantage of the NCI registry for our analysis—relative to other clinical trials databases such as the *NDA Pipeline* data or the Pharmaprojects data—is the fact that the NCI registry explicitly lists which groups of patients (as defined by cancer type and stage at diagnosis) are eligible to participate in each clinical trial. This feature enables us to construct a measure of the number of clinical trials in which different groups of patients (as defined by cancer type and stage) are eligible to enroll, providing a metric of firms' willingness to investigate candidate drugs on different groups of patients.

The NCI registry includes a handful of clinical trials with dates prior to 1973; we focus on trials from 1973 forward for consistency with the SEER registry data (which starts in 1973) and have data on trials through 2011. For a subset of clinical trials in our data, we observe whether the clinical trial was publicly sponsored or privately sponsored.

C. *FDA Drug Approvals Data*

While our main analysis focuses on the NCI clinical trials data, we also examine a dataset of the 71 FDA approved oncology drugs from 1990–2002 from Johnson, Williams, and Pazdur (2003). For 39 of these 71 drug approvals, we were able to hand-collect data on whether a surrogate endpoint was used, as well as the cancer and stage for which the drug was approved, from the Drugs@FDA database.[36]

[35] Clinical trials are also used as a measure of R&D investments in Finkelstein (2004).

[36] Thirty-two of the approvals in the Johnson, Williams, and Pazdur (2003) list had no information available in the Drugs@FDA database on the indication for which the drug was approved, and we are not aware of an alternative source for this data. Given the coarse stage information that is included in the indication descriptions, we code stage for the drug approval data as "early," "late," or "not specified" (rather than localized, regional, and distant). In our sample of 39 approvals, 4 are coded as early stage, 25 are coded as late stage, and 10 are coded as not specified.

Table 1—Summary Statistics: Cancer-Stage Data

	Mean	Median	Standard deviation	Minimum	Maximum
Number of clinical trials, 1973–2011	945	556	1,015	221	7,385
Number of drug approvals, 1990–2002	0.507	0	1.221	0	7
Five-year survival rate, cases diagnosed 1973–2004	0.377	0.383	0.249	0.006	0.945
Number of diagnoses (1,000s), 1973–2009	12.423	3.159	29.429	0.010	252.593
Estimated years of life lost (1,000s), 1973–1983	114.433	35.663	233.576	0.583	1,658.804
Share of trials privately financed	0.258	0.265	0.062	0.122	0.507

Notes: This table shows summary statistics for our cancer-stage level data. The level of observation is the cancer-stage. The clinical trials data is available from 1973–2011. The drug approvals data is available from 1990–2002. The SEER data starts in 1973 and ends in 2009, which is why the number of diagnoses variable is measured over that time period. The five-year survival rate is calculated over patients diagnosed between 1973–2004, the cohorts for which five-year survival is uncensored as of 2009. The life years lost measure is calculated on cohorts diagnosed from 1973–1983 to minimize censoring, as explained in the text. As explained in the text, we suspect that sponsorship data is more likely to be reported for publicly funded trials relative to privately financed trials. All variables have 201 observations except for the life lost measure which has 192, because 9 cancer-stages had no patients diagnosed between 1973–1983. For details on the sample, see the text and online Data Appendix.

D. *Summary Statistics for Cancer-Stage Level Data*

We aggregate the patient-level cancer registry data and cancer clinical trials data into cancer-stage level observations. Our sample is constructed based on the 80 cancer types underlying the SEER site recodes, and the three non-in situ stages underlying the SEER historic stage A variable: localized, regional, and metastatic. After accounting for the details of how staging varies across cancers, our benchmark cancer-stage sample includes 201 observations: 60 cancers appear for all 3 stages (localized, regional, distant; 180 observations); prostate cancer is coded by SEER into 2 stages (localized/regional, distant; 2 observations); and 19 cancers are unstaged by SEER and hence only appear as 1 observation (19 observations).

Table 1 presents some basic summary statistics on our cancer-stage level data. Between 1973–2011, an average cancer-stage had roughly 1,000 clinical trials, but this average masks tremendous variation—ranging from a minimum of around 200 to a maximum of over 7,000. Between 1990–2002, the median cancer-stage had no drugs approved, ranging to a maximum of 7. Using the number of patients diagnosed with a given cancer-stage as a rough measure of market size, on average a cancer-stage has around 12,000 diagnoses in SEER catchment areas between 1973–2009, ranging from 100 to over 250,000. On average, the five-year survival rate (defined for cohorts diagnosed between 1973–2004, all uncensored cohorts) is 38 percent, but ranges from almost 0 to 94 percent. Finally, among trials reporting sponsorship data, around 75 percent report being publicly financed. Given that sponsorship data is missing for approximately one-half of our sample, it is difficult to know whether this is an accurate picture, or whether sponsorship is more likely to be reported for publicly funded trials relative to privately financed trials. While such systematic under-reporting of private sponsorship data could bias measurement of the level or share of trials that are privately financed, we do not expect such

under-reporting to vary systematically with our survival time measure: in which case, our empirical tests using sponsorship measures should still be valid.

III. Descriptive Analysis

A. *Analysis by Stage*

Panel A of Figure 1 plots two measures of clinical trial activity for each stage of cancer from 1973 to 2011 against the five-year survival rate of patients diagnosed with that cancer-stage from 1973 to 2004. Whereas metastatic cancer patients have a five-year survival rate of around 10 percent, the five-year survival rate for regional patients is around 50 percent, and for localized patients is about 70 percent. The left-hand-side axis plots the corresponding number of clinical trials enrolling patients of each stage: metastatic cancer patients were the focus of nearly 12,000 clinical trials in our data, whereas regional cancer patients were the focus of around 10,000, and localized patients around 6,000.

Dating back at least to Schmookler (1966), economists have hypothesized that market size would be an important determinant of the level of R&D investments. Several recent papers have provided evidence for this idea in the context of the pharmaceutical industry (Acemoglu and Linn 2004; Finkelstein 2004; Trusheim and Berndt 2012; Dubois et al. forthcoming). In our setting, a rough proxy for market size is the number of life-years lost from cancer. The right-hand-side axis plots the number of clinical trials enrolling patients of each stage, divided by the number of life-years lost from that stage as a rough adjustment for market size.[37] This adjustment does little to change the basic pattern.

Panel B of Figure 1 adds clinical trial counts for three other categories of disease for which the five-year survival rate is difficult to define: prevention trials, in situ cancers, and recurrent cancers. The bars are roughly positioned in order of increasing survival rates, for comparability with panel A of Figure 1. Very few clinical trials aim to prevent cancer (less than 500) or to treat in situ cancers (less than 200). In contrast, recurrent cancers have more trials than any other stage of disease (over 17,000).

B. *Analysis by Cancer-Stage: Full Sample*

Figure 2 illustrates the relationship between our two key variables of interest in the full sample of cancer-stage observations: the five-year survival rate, and the number of clinical trials enrolling patients of that cancer-stage.[38] For cancer-stages

[37] As described in Section II, life-years lost is measured as age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied times market size.

[38] To give a visual sense of the data for a few major cancers, online Appendix Figure D.1 plots the relationship between the five-year survival rate and clinical trial activity for the "big four" cancers: breast, colon, lung, and prostate. Online Appendix Figure D.1(a) plots the number of clinical trials enrolling patients of each cancer-stage, which decline with increases in the five-year survival rates. The points are labeled with the relevant cancer and stage, which enables a visual analysis of this relationship either within cancers (e.g., metastatic versus localized breast cancer) or within stages (e.g., localized lung cancer versus localized colon cancers). Online Appendix Figure D.1(b) adjusts the clinical trial count by the number of patients diagnosed as a rough adjustment for market size. Here, the downward-sloping relationship between the survival rate and R&D investments is much more clearly visible.

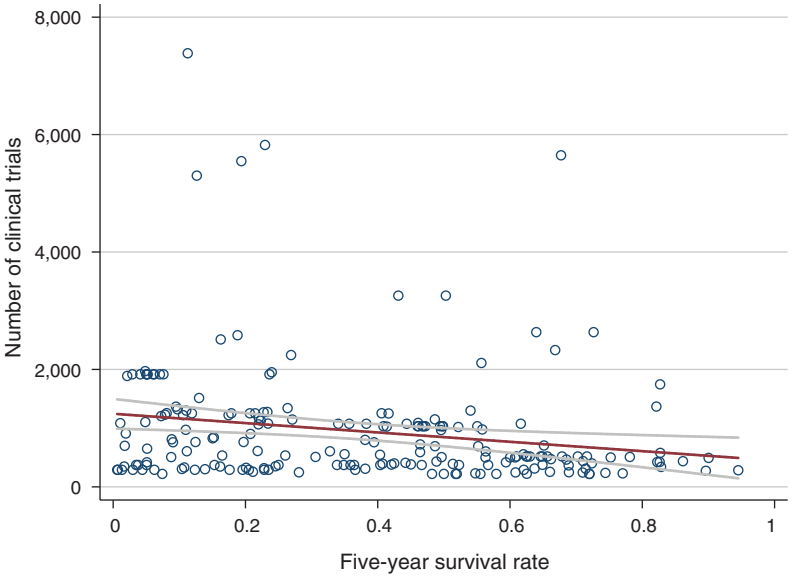

FIGURE 2. SURVIVAL TIME AND R&D INVESTMENTS: CANCER-STAGE DATA

Notes: This figure shows the relationship between the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and the number of clinical trials enrolling patients of each cancer-stage from 1973–2011. Note that because we here count the number of clinical trials patients of each cancer-stage are eligible to enroll in, a higher count of trials appears here than in Figure 1 because many trials enroll patients of more than one cancer-stage type. The level of observation is the cancer-stage. For details on the sample, see the text and online Data Appendix.

with low survival rates, there is tremendous variation in the number of clinical trials, with some cancer-stages having a very high number of trials. In contrast, for cancer-stages with high survival rates, the distribution of clinical trial counts tends to be more compressed, and smaller in magnitude. The combination of these two patterns generates the downward-sloping relationship between the survival rate and R&D investments.

Table 2 formalizes this relationship between clinical trial activity and the five-year survival rate in a regression framework. For cancer-stage observation *cs*, we estimate the following:

$$Y_{cs} = \alpha + \beta S_{cs} + \lambda' X_{cs} + \varepsilon_{cs}. \tag{10}$$

The number of clinical trials Y for the cancer-stage is the outcome variable, and the coefficient on the survival rate variable S is the main estimate of interest. We investigate the robustness of this relationship by conditioning on various covariates X, described below. Reflecting the count nature of the clinical trials outcome, we show estimates from quasi-maximum likelihood Poisson models.[39] We report heteroskedasticity-robust standard errors clustered at the cancer level.

[39] Estimates from ordinary least squares models using the log of the number of clinical trials as the dependent variable are essentially identical (estimates not reported).

Table 2—Survival Time and R&D Investments: Cancer-Stage Data

	Number of clinical trials (mean = 945)		
	(1)	(2)	(3)
Five-year survival rate	−0.868***	−1.113***	−0.930***
	(0.319)	(0.286)	(0.286)
log(Market size)	—	0.243***	—
		(0.055)	
log(Life-years lost)	—	—	0.282***
			(0.068)

Notes: This table shows the relationship between the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and the number of clinical trials enrolling patients of that cancer-stage from 1973–2011. The level of observation is the cancer-stage. Estimates are from quasi-maximum likelihood Poisson models. Standard errors are clustered at the cancer level. "Market size" denotes the number of patients diagnosed with that cancer-stage between 1973–2009. "Life-years lost" denotes age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied by market size. The number of observations is 201 in columns 1 and 2, and 192 in column 3, because 9 cancer-stages had no patients diagnosed between 1973–1983. For details on the sample, see the text and online Data Appendix.

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

Column 1 of Table 2 reports the raw correlation between the five-year survival rate and the number of clinical trials. The estimated coefficient implies that a 10 percentage point increase in the five-year survival rate is associated with a 8.7 percent decrease in R&D investments. Column 2 adds a rough market size control (measuring the log of the number of patients diagnosed with that cancer-stage), which does not substantively change the estimate of interest. This market size variable is clearly an imperfect measure of demand. As one attempt to refine this measure, we construct a measure of life lost at the individual level—measured as age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years. At the individual level, this measure attempts to proxy for willingness to pay, and summed across all individuals diagnosed with a given cancer-stage it may provide a more accurate measure of market size. Column 3 shows that the survival time-R&D correlation is similar if we condition on this alternative measure of market size. In Section IVA, we investigate the concern of unobserved heterogeneity in demand more directly. Figure 3 presents the visual analog of these regression specifications, residualizing the survival rate using our two measures of market size.

In an online Appendix, we present a number of additional robustness checks on this correlation. First, we ask whether the survival time-R&D correlation is similar when estimated within cancers (cancer fixed effects) and within stages (stage fixed effects). Online Appendix Table D.1 shows that the magnitude of the survival time-R&D correlation is quite similar after conditioning on cancer fixed effects, stage fixed effects, or both.[40] Second, we ask whether the survival time-R&D correlation

[40] For comparability, we omit the 19 unstaged cancers from the sample in this table since these observations do not identify the relationship of interest once we include cancer fixed effects and by definition unstaged cancers do not correspond to localized, regional, or metastatic stage definitions. Online Appendix Figure D.2 shows

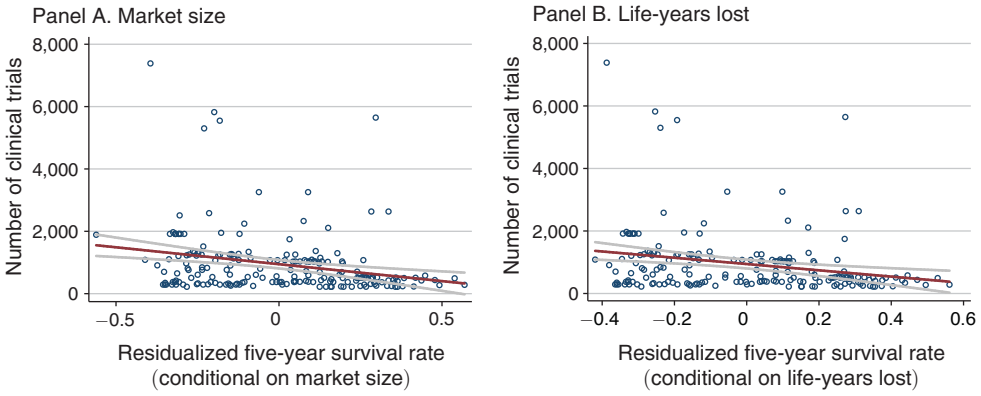

FIGURE 3. SURVIVAL TIME AND R&D INVESTMENTS: RESIDUALIZED CANCER-STAGE DATA

Notes: This figure shows the relationship between residualized versions of the five-year survival rate among patients diagnosed with that cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and the number of clinical trials enrolling patients of each cancer-stage from 1973–2011. The level of observation is the cancer-stage. Panel A residualizes market size; panel B residualizes life-years lost. Market size denotes the inclusion of a covariate measuring the number of patients diagnosed with that cancer-stage between 1973–2009. Life-years lost is measured as age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied by market size. For details on the sample, see the text and online Data Appendix.

is robust to alternative measures of patient survival time. Online Appendix Table D.2 shows that the estimated magnitude is quite similar using the one-year survival rate, as well as several parameterizations of a "pre-period" survival rate (1973 survival in years, the 1973 one-year survival rate, and the 1973 five-year survival rate). We focus on the five-year survival rate measured over a longer time period because we expect the survival rate to be more accurately measured on a larger sample, but the estimated magnitudes are not statistically distinguishable. Third, we investigate the robustness of the survival time-R&D correlation in various subsamples of the data in online Appendix Table D.3. The estimated correlation is quite similar, for example, if metastatic cancers are excluded—suggesting that the observed correlation does not only reflect a high level of research on end-of-life patients. Finally, online Appendix Table D.4 confirms that the survival time-R&D correlation also holds in our sample of approved drugs.

IV. Interpreting the Correlation between Survival Time and R&D Investments

Section III documents what is, to the best of our knowledge, a new fact: R&D investments on cancer treatments are strongly negatively correlated with commercialization lags, as proxied by survival rates. This fact is consistent with the idea that private firms may underinvest in long-term research, because we observe lower levels of R&D investment on inventions that require longer commercialization lags. However, by itself this fact is difficult to interpret for two reasons. First, other factors—such as heterogeneity in demand and heterogeneity in the costs of

residualized scatterplots corresponding to the regression specifications presented in online Appendix Table D.1 on this same sample.

R&D—could generate the same qualitative pattern. On demand, while our regression analysis conditioned on indirect demand measures—such as market size and life-years lost—these variables may not capture the complex ways in which the survival rate may correlate with demand (see, e.g., Hammitt and Haninger 2010; Philipson et al. 2010). On costs, it could be, for example, that the science of treating cancer-stages with long commercialization lags is more difficult, and that observed low R&D investments reflect a paucity of scientific opportunities. Second, even if this correlation does reflect a causal effect of commercialization lags on R&D investments, it need not be evidence of a distortion, because the social planner is also more likely to pursue research projects that can be completed more quickly.

To address these concerns, in this section we document estimates from two additional empirical tests. First, in Section IVA we document causal evidence that shortening commercialization lags increases R&D investments. This evidence suggests, for example, that heterogeneity in demand is unlikely to explain the cross-sectional relationship between survival time and R&D. However, this test leaves open the possibility that the social planner and private firms symmetrically respond to commercialization lags, and thus does not provide direct evidence of a distortion. Our second empirical test in Section IVB fills this gap by directly contrasting public and private R&D investments. Section IVC documents supporting qualitative evidence from historical case studies of FDA-approved chemoprevention drugs, which suggest that surrogate endpoints and public subsidies have played a key role in the development of chemoprevention drugs. Taken together, this body of evidence provides support for the idea that commercialization lags distort private R&D investments.

A. *Investigating Surrogate Endpoints*

If heterogeneity in demand for treatments or a paucity of scientific opportunities were driving the survival time-R&D correlation, the observed correlation should be independent of whether surrogate endpoints are used. In contrast, our model predicts that surrogate endpoints should make the survival time-R&D correlation less negative (Proposition 4). In this section, we document that there is *not* a negative survival time-R&D correlation in the sample of cancers allowed to use surrogate endpoints.[41]

As discussed by the US Food and Drug Administration (2007) and Johnson, Williams, and Pazdur (2003), the most clearly established non-mortality related endpoint is "complete response" for leukemias. A historical example is helpful in illustrating why this surrogate endpoint has been useful. Mukherjee (2010) chronicles Sidney Farber's 1948 discovery of chemotherapy, which was made in the context of leukemia (Farber et al. 1948). While investigating folic acid deficiencies, Farber hypothesized that folic acid antagonists could be of value in treating cancer patients—paving the way for the development of modern chemotherapy drugs. Mukherjee's (2010) account of Farber's discovery argues that Farber was naturally inclined to test folic acid antagonists in the context of leukemia because white blood cell count monitoring offered an accepted method for testing whether the drug was

[41] As highlighted above, surrogate endpoints enable shorter trials, so this test does not provide direct evidence of a distortion; we address this issue in a separate test in Section IVB.

effective in pushing the disease into remission. While monitoring technologies have clearly progressed since Farber's time, remission criteria in leukemias are still based on the same idea of blood cell counts and related bone marrow measures—outcomes which are generally agreed to closely correlate with improved survival. In addition to being used for monitoring, such measures have also been accepted by the FDA as the basis for approval of drug treatments for hematologic malignancies (leukemias and lymphomas; see Pazdur 2000 and Johnson, Williams, and Pazdur 2003).[42]

To investigate the effects of surrogate endpoints on R&D activity, we use both our clinical trials data and our drug approvals data.[43] In the sample of approved drugs, we can confirm that hematological malignancies are more likely to be approved on the basis of surrogate endpoints: in our data, 92 percent of drugs approved by the FDA for hematological malignancies were approved on the basis of surrogate endpoints, relative to 53 percent of non-hematological malignancies.

We use these data to test three predictions of our model that relate to commercialization activity. First, part (i) of Proposition 4 predicts that the use of surrogate endpoints should increase commercialization activity. To test this prediction, we ask whether—conditional on the five-year survival rate—hematological malignancies have a larger number of clinical trials. The estimated coefficient in column 1 of panel A in Table 3 suggests yes: interpreting the coefficient on this binary independent variable ($\beta = 0.753$) suggests a 112 percent increase in clinical trials for hematological malignancies relative to non-hematological malignancies $\left((e^{\beta} - 1) \cdot 100 \approx 112 \text{ percent}\right)$. This pattern is robust to the inclusion of controls for market size (columns 2 and 3). This result is consistent with the analysis of Trusheim and Berndt (2012), who observe that hematological malignancies have a larger number of clinical trials than would be expected based on their market size.

Second, Part 3 of Proposition 4 predicts that, if survival time is independent of the time required to show impacts on the surrogate endpoint, then the use of surrogate endpoints should reduce the negative relationship between survival time and R&D investments. Third, in cases where surrogate endpoints do *not* decrease commercialization lag, our model implies that surrogate endpoints should *not* change R&D incentives. That is, for cancers that have a short commercialization lag even in the absence of using a surrogate endpoint, the option to use a surrogate endpoint should not change R&D incentives. Empirically, this means that we expect hematologic and non-hematologic cancers to have similar levels of R&D for the set of cancers that have short commercialization lags even in the absence of using surrogate endpoints (that is, for low survival time cancers).

[42] Based on our reading of these FDA writings, our understanding is that both scientists and regulators have viewed the surrogate endpoints used for hematologic cancers as valid and uncontroversial. Although far from definitive, our empirical evidence in Section V is consistent with this view, suggesting that the additional R&D investments induced by the use of these surrogate endpoints have translated into improved survival gains.

[43] We use this drug approvals data in part to address a measurement error concern that could arise with our clinical trials data. Namely, the automated coding of our clinical trials data into cancer types (as detailed in online Appendix B) could be less reliable for hematologic malignancies relative to other forms of cancer if text searches for organ names ("breast," "prostate," etc.) are more accurate than our text searches for different forms of leukemias and lymphomas (the names of which tend to be more complex). While we aimed for the highest possible accuracy in cleaning the clinical trials data, because of the large sample size our cleaning of that data must be automated. In contrast, because there are a small number of drug approvals, we can hand-code the cancer types relevant to each drug approval, reducing concerns about measurement error.

Table 3—Surrogate Endpoints, Survival Time, and R&D Investments

	(1)	(2)	(3)
Panel A. Level of R&D, dependent variable: number of clinical trials (mean = 945)			
Five-year survival rate	−0.865***	−1.108***	−0.933***
	(0.310)	(0.284)	(0.283)
(0/1: hematologic)	0.753***	0.578***	0.466**
	(0.185)	(0.176)	(0.201)
log(Market size)	—	0.231***	—
		(0.057)	
log(Life-years lost)	—	—	0.261***
			(0.073)
Panel B. Composition of R&D, dependent variable: number of clinical trials (mean = 945)			
(Five-year survival rate) × (0/1: hematologic)	2.266***	2.140***	1.963***
	(0.408)	(0.541)	(0.613)
Five-year survival rate	−1.122***	−1.309***	−1.133***
	(0.343)	(0.297)	(0.303)
(0/1: hematologic)	−0.077	−0.216	−0.261
	(0.189)	(0.228)	(0.252)
log(Market size)	—	0.226***	—
		(0.056)	
log(Life-years lost)	—	—	0.253***
			(0.073)

Notes: This table shows two analyses of how cancer R&D differs on hematologic malignancies relative to other cancers, as a way of shedding light on how surrogate endpoints—which are more commonly used for hematologic malignancies—affect R&D investments. Panel A regresses the number of clinical trials enrolling patients of that cancer-stage from 1973–2011 on the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored) and an indicator for hematological malignancies. Panel B regresses the number of clinical trials enrolling patients of that cancer-stage from 1973–2011 on the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004, an indicator for hematological malignancies, and an interaction between these two variables. The level of observation is the cancer-stage. Estimates are from quasi-maximum likelihood Poisson models. Standard errors are clustered at the cancer level. "Market size" denotes the number of patients diagnosed with that cancer-stage between 1973–2009. "Life-years lost" denotes age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied times market size. The number of observations is 201 in columns 1 and 2, and 192 in column 3, because 9 cancer-stages had no patients diagnosed between 1973–1983. For details on the sample, see the text and Data Appendix.

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

To test these second and third predictions we estimate the following specification, where H_c is an indicator for hematological malignancies

$$Y_{cs} = \alpha + \beta S_{cs} \cdot H_c + \gamma H_c + \delta S_{cs} + \lambda' X_{cs} + \varepsilon_{cs}. \tag{11}$$

Panel B in Table 3 presents these estimates. In contrast to the negative correlation between the five-year survival rate and the number of clinical trials for non-hematological malignancies (δ), we estimate a positive coefficient on the interaction term (β)—consistent with the second prediction of our model.[44] This estimate

[44] Interpreting the interaction term in this nonlinear model requires transforming the coefficient; the interaction coefficient of 2.266 in the first row of panel B implies that an increase in the five-year survival rate of 10 percentage points predicts an increase in the number of trials for hematologic cancers that is greater than that of non-hematologic cancers by 300 trials (about 30 percent relative to the mean), and applying the delta method to

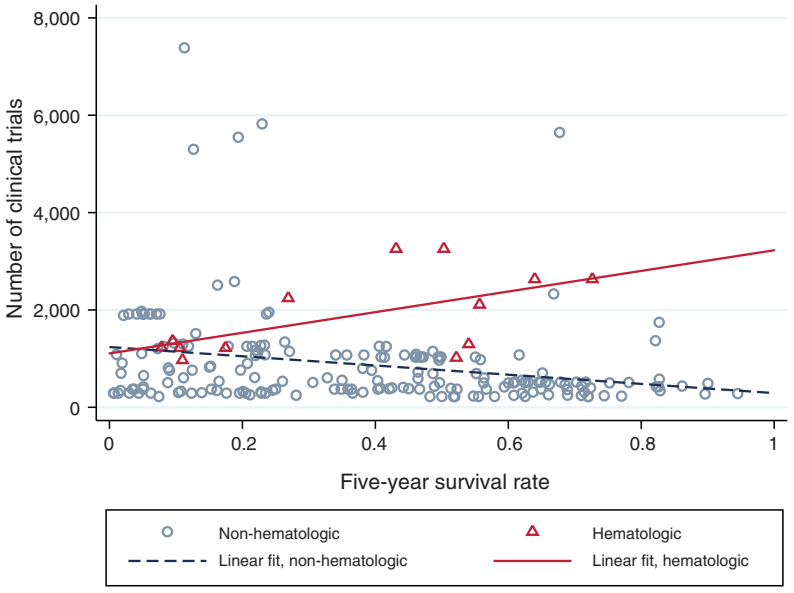

FIGURE 4. SURROGATE ENDPOINTS, SURVIVAL TIME, AND R&D INVESTMENTS

Notes: This figure shows the relationship between five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and number of clinical trials enrolling patients of each cancer-stage from 1973–2011, separately for hematologic and non-hematologic cancers. The level of observation is the cancer-stage. For details on the sample, see the text and online Data Appendix.

is robust to the inclusion of controls for market size (columns 2 and 3). This contrast in survival time-R&D correlations across hematologic and non-hematologic cancers is presented graphically in Figure 4.[45]

With respect to the third prediction of our model, we find that the estimated coefficient on the indicator variable for hematologic cancers is, statistically speaking, zero, and also relatively small in magnitude. In addition to being consistent with our model, this result is also important as a test of a key assumption underlying this counterfactual exercise: namely, that hematologic cancers and non-hematologic cancers would have similar R&D investments but for the more frequent use of surrogate endpoints for hematologic cancers. A priori, hematologic and non-hematologic cancers are very different for many reasons—for example, the science of treating hematologic cancers might be simpler for some reason. However, to the extent that such differences are common across all hematologic cancers, hematologic cancers with low five-year survival rates should have higher levels of R&D investments than do non-hematologic cancers with low five-year survival rates. But that is not what we see in the data: rather, hematologic and non-hematologic cancers have similar levels of R&D investments for the patient groups where surrogate endpoints should not change R&D incentives. This evidence is consistent with the "all else equal" assumption behind this hematologic/non-hematologic comparison.

obtain a standard error for this interaction term provides a *t*-statistic of 5.99. Figure 4 gives an alternative sense of the magnitude of the coefficients obtained from a linear model.

[45] Online Appendix Table D.5 shows that this pattern of results also holds in the drug approvals data.

What can we learn from this counterfactual exercise? We draw two conclusions. First, from the perspective of testing the model, our estimates are consistent with the idea that neither unobserved heterogeneity in demand nor a paucity of scientific opportunities is driving the observed negative survival time-R&D correlation in the full sample. Second, from a policy perspective our estimates support the idea (analyzed in Proposition 4) that valid surrogate endpoints may increase R&D investments, particularly on long-horizon R&D investments. The key caveat to interpreting this evidence as a test of our theoretical model is that because surrogate endpoints change the length of clinical trials, both the social planner and private firms should choose to increase research investments. Hence, this test does not provide direct evidence of a distortion; our second empirical test in Section IVB fills this gap by directly contrasting public and private R&D investments.

In online Appendix A, we use this hematologic/non-hematologic comparison to provide a rough back-of-the-envelope estimate of the semi-elasticity of R&D investment with respect to a one-year change in commercialization lag: $\partial(\text{R\&D investment})/\partial(\text{commercialization lag})$.[46] Our main estimates of this semi-elasticity range between 7–23 percent.[47] It is worth noting that this elasticity is itself of policy relevance, as an input into how firms would be expected to respond to decreases in commercialization lags as provided by mechanisms such as FDA priority review vouchers (Ridley, Grabowski, and Moe 2006).

B. *Investigating Publicly Financed Clinical Trials*

Our second empirical test directly contrasts public and private R&D investments. Consistent with our theoretical model, we document that commercialization lags reduce both public and private R&D investments. But also consistent with our model—and consistent with the conjectured distortion—we will see that the commercialization lag-R&D correlation is quantitatively and statistically significantly more negative for privately financed trials relative to publicly financed trials.

As a first analysis of our trial sponsorship data, panel A of Figure 5 presents the cumulative distribution functions (CDF) of clinical trial lengths in the trial-level data, separately for privately financed and publicly financed trials. The privately financed CDF lies above the publicly financed CDF at almost every clinical trial length. The vertical line at 20 years denotes the length of the fixed patent term: consistent with the idea that the patent system should offer zero incentive to develop drug compounds that take longer than 20 years to develop, very few trials in our data have a reported length of 20 years or longer. Of the approximately 120 clinical trials longer than 20 years that have non-missing data on sponsorship, essentially 100 percent are publicly funded.[48]

[46] As described in online Appendix A, obtaining this semi-elasticity estimate requires scaling our estimate of how R&D investment changes in response to a change in the five-year survival rate ($\partial(\text{R\&D investment})/\partial(\text{5-year survival rate})$) by an estimate of how a change in the five-year survival rate translates into a change in commercialization lag ($\partial(\text{commercialization lag})/\partial(\text{5-year survival rate})$).

[47] We are not aware of any existing estimates against which this estimate can be compared.

[48] The longest privately financed trial in our data lasts 18.66 years, with the exception of six trials that are reported to last longer than 60 years. We suspect that these six trials have typographical errors in their start dates, but have not yet heard back from the sponsor (Bristol-Myers Squibb) in an inquiry on this point. If these six trials

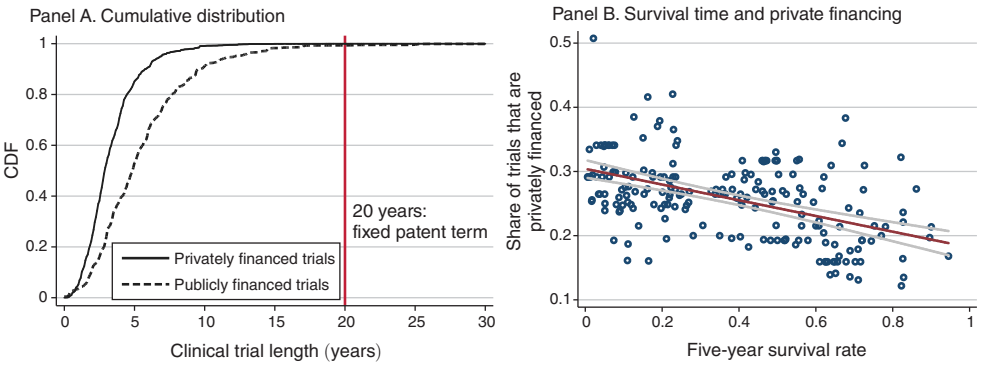

FIGURE 5. SURVIVAL TIME AND FINANCING OF CLINICAL TRIALS

Notes: This figure shows two analyses of how public and private financing of clinical trials differ. Panel A plots the cumulative distribution function of clinical trial length in years, omitting the handful of observations with length greater than 30 years for improved readability. The level of observation is the clinical trial. The vertical line at 20 years denotes the length of the fixed patent term. Panel B plots the relationship between the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and the share of clinical trials enrolling patients of that cancer-stage from 1973–2011 that were privately financed. The level of observation is the cancer-stage. For details on the sample, see the text and online Data Appendix.

Panel B of Figure 5 provides a second analysis of this sponsorship data, plotting the relationship between the five-year survival rate and the share of clinical trials enrolling patients of that cancer-stage which are privately financed.[49] The downward-sloping relationship is quantified in panel A of Table 4: a 10 percentage point increase in the five-year survival rate is associated with a 1.2 percent decrease in the share of clinical trials that are privately financed. The magnitude of this coefficient is quite similar conditional on our market size controls (columns 2 and 3).

Panel B of Table 4 presents estimates from a second test of how public and private R&D investments differ. Estimating equation (10) separately on the sample of publicly financed trials and on the sample of privately financed trials, we would like to compare the estimated β coefficients to see whether the correlation between survival time and clinical trial activity is smaller in the sample of publicly financed trials relative to the sample of privately financed trials. Formally equivalent to estimating these two regressions separately is estimating a stacked regression where the unit of observation is a cancer-stage-type *cst* (where type is either privately financed or publicly financed)

$$(12) \qquad Y_{cst} = \alpha + \beta S_{cs} \cdot T_t + \gamma T_t + \delta S_{cs} + \lambda' X_{cs} \cdot T_t + \varepsilon_{cst}.$$

Our T_t variable is defined as an indicator which equals 1 for observations counting privately financed trials, and equals 0 for observations counting publicly financed trials. The coefficient of interest β measures the difference in the survival

have typographical errors as we expect, then 100 percent of the trials with non-missing data on sponsorship that are longer than 20 years are publicly funded.

[49] In interpreting the scale of the graph, recall that as noted in Section IID we suspect that sponsorship data is more likely to be reported for publicly funded trials relative to privately financed trials.

Table 4—Survival Time and Financing of Clinical Trials

	(1)	(2)	(3)
Panel A. Share of clinical trials that are privately financed (*mean* = 0.258)			
Five-year survival rate	−0.122***	−0.134***	−0.119***
	(0.016)	(0.017)	(0.014)
log(Market size)	—	0.009 ***	—
		(0.003)	
log(Life-years lost)	—	—	0.008***
			(0.003)
Panel B. Number of clinical trials (*mean* = 244)			
(Five-year survival rate) × (0/1: private)	−0.436***	−0.500***	−0.470**
	(0.166)	(0.171)	(0.195)
Five-year survival rate	−0.866***	−1.097***	−0.932***
	(0.314)	(0.287)	(0.285)
(0/1: private)	−0.681***	−0.723***	−0.833***
	(0.062)	(0.054)	(0.081)
log(Market size)	—	0.230 ***	—
		(0.063)	
log(Market size) × (0/1: private)	—	0.003 ***	—
		(0.002)	
log(Life-years lost)	—	—	0.257***
			(0.076)
log(Life-years lost) × (0/1: private)	—	—	0.001***
			(0.000)

Notes: This table shows two analyses of how public and private financing of clinical trials varies with patient survival time. Panel A shows the relationship between the five-year survival rate among patients diagnosed with each cancer-stage between 1973–2004 (the cohorts for which five-year survival is uncensored), and the share of clinical trials enrolling patients of that cancer-stage from 1973–2011 that were privately financed; the level of observation is the cancer-stage, and estimates are from ordinary least squares (OLS) models. Panel B shows the relationship between the five-year survival rate and the number of publicly/privately financed clinical trials enrolling patients of that cancer-stage from 1973–2011; the level of observation is the cancer-stage-sponsor (where sponsor is either public or private), and estimates are from quasi-maximum likelihood Poisson models. Standard errors are clustered at the cancer level. "Market size" denotes the number of patients diagnosed with that cancer-stage between 1973–2009. "Life-years lost" denotes age-gender-year specific life expectancy (in the absence of cancer) in the year of diagnosis, less observed survival time in years, averaged over patients diagnosed with that cancer-stage between 1973–1983 (to minimize censoring) multiplied by market size. The number of observations is 201 in columns 1 and 2 of panel A, 402 (= 201 × 2 sponsor types) in columns 1 and 2 of panel B, 192 in column 3 of panel A, and 384 (= 192 × 2 sponsor types) in column 3 of panel B, because 9 cancer-stages had no patients diagnosed between 1973–1983. For details on the sample, see the text and online Data Appendix.

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

time-clinical trial activity correlation observed for privately financed trials relative to that observed for publicly financed trials.

These estimates are presented in panel B of Table 4. The negative β estimate implies that the relationship between the five-year survival rate and R&D investments is more negative for privately financed trials relative to publicly financed trials—consistent with what we expected based on the analyses in panel B of Figure 5. Interpreting the point estimate in column 1 suggests that a 10 percentage point increase in the five-year survival rate results in an additional 4.4 percent decrease in privately financed clinical trials, in addition to the 8.6 percent decrease observed for publicly financed clinical trials. These estimates imply that the relationship between survival time and clinical trial activity is on the order of 35 percent

larger for privately financed clinical trials relative to publicly financed clinical trials ($4.4/(4.4 + 8.6) \approx 35$ percent). The point estimates and their ratio are quite stable across specifications adding our market size controls (columns 2 and 3).

We wish to make two remarks concerning these estimates. First, this public-private contrast is consistent with two potential models of public sector decision making: the public sector could have a different objective function than the private sector (as in our model), or the public sector could be compensating for underinvestment by the private sector. Both models are consistent with the existence of a distortion, and thus have the same qualitative interpretation, but the quantitative interpretation of the estimates would differ across the two models. Second, to the extent that a large share of publicly financed clinical trials investigate new uses of existing drugs, publicly financed trials may be constrained by science to mirror privately financed R&D investments.

C. *Historical Case Studies of FDA-Approved Chemoprevention Drugs*

As a complement to our empirical analyses, we also document qualitative (case study) evidence on what motivated the development of existing chemoprevention drugs. Because cancer prevention trials typically examine cancer incidence as an outcome variable, we expect cancer prevention technologies to generally require long trials and thus to also be subject to our conjectured distortion. We start with the list of all six FDA approved chemoprevention drugs compiled by Meyskens et al. (2011). Our qualitative investigation of the history of these FDA drug approvals suggests that all six of these approvals either relied on the use of surrogate endpoints, or were approved on the basis of publicly financed clinical trials. Table 5 documents a summary of our work in online Appendix E, which provides documentation for this assertion, and we here focus on briefly summarizing two of the case studies. First, the drug Tamoxifen was FDA approved for several cancer indications while on-patent; later, a publicly funded clinical trial supported the 1998 FDA approval of Tamoxifen as a chemoprevention agent, preventing breast cancer incidence in high-risk groups. Second, the recent FDA approval of cervical cancer vaccines relied on the use of human papillomavirus (HPV) incidence as a surrogate endpoint for cervical cancer incidence. Hence, the evidence from these case studies is quite consistent with the conjectured distortion: we expect cancer prevention trials to have long commercialization lags, and no cancer prevention technologies have been privately developed without relying on surrogate endpoints.

V. Estimating the Value of Life Lost Due to Commercialization Lags

In this section, we leverage our surrogate endpoint variation from Section IVA to estimate counterfactual improvements in cancer survival rates that would have been observed if commercialization lags were reduced.[50] Importantly, this exercise should not be interpreted as quantifying the size of our conjectured distortion, because as discussed surrogate endpoints generate social value beyond eliminating

[50] While we would ideally quantify R&D-induced improvements in both morbidity and mortality, given data constraints we here focus on estimating the extent to which R&D increases patient survival.

Table 5—Historical Case Studies of FDA-Approved Chemoprevention Drugs

	Approval indication	Surrogate endpoint used?	Primarily publicly funded?
BCG (Bacillus Calmette-Guérin)	bladder carcinoma in situ	no	yes
Diclofenac	squamous cell carcinomas	yes	no
Celecoxib	familial adenomatous polyposis (FAP)-related cancers	yes	no
Photofrin	esophageal carcinoma	yes	no
Tamoxifen	breast cancer	no	yes
Cervical cancer vaccines	cervical cancer	yes	no

Notes: This table summarizes our qualitative investigation of the history of all six FDA drugs approved as cancer prevention (chemoprevention) drugs. The key point of this table is to illustrate that all six of these approvals either relied on the use of surrogate endpoints, or were approved on the basis of publicly financed clinical trials: no chemoprevention drugs have been privately developed in the absence of relying on surrogate endpoints. See the descriptions in Section IVC and online Appendix E for more details.

the distortion. As with our back-of-the envelope estimates of the semi-elasticity of R&D investment with respect to changes in the commercialization lag, this exercise is directly policy relevant as an input into how firms would be expected to respond to decreases in commercialization lags as provided by mechanisms such as the application of valid surrogate endpoints or FDA priority review vouchers (Ridley, Grabowski, and Moe 2006).

Figure 6 illustrates how we use variation in surrogate endpoints (across hematologic and non-hematologic cancers) to estimate counterfactual survival gains from 1973–2003. Panel A of Figure 6 illustrates our conceptual framework. If there had been no survival improvements between 1973 and 2003, all cancer-stage observations would locate along the 45-degree line ("no progress line"); in contrast, if all cancer-stages had been cured between 1973 and 2003, all cancer-stage observations would locate along the horizontal line where 2003 survival rates equal 1 ("cure cancer line"). As discussed in Section IVA, we expect two patterns to emerge when contrasting survival improvements across for hematologic and non-hematologic cancers. First, survival improvements should be similar for hematologic and non-hematologic cancers in cases where surrogate endpoints do not shorten commercialization lags (that is, for cancers with low 1973 five-year survival rates). Second, the difference in survival improvements between hematologic and non-hematologic cancers should increase in commercialization lag (that is, increase in the 1973 five-year survival rate). Reflecting these predictions, the line marked "non-hematologic cancers" coincides with the line marked "hematologic cancers" at 0 percent survival, and the gap between the two lines increases as commercialization lag increases.

Panel B plots the observed 2003 five-year survival rates against the 1973 five-year survival rates. Strikingly, the data matches our illustrative figure in panel A remarkably well. In particular, the linear fit lines for hematologic cancers and non-hematologic cancers meet for cancers with a very low 1973 five-year survival rate; the linear fit for hematologic cancers is close to a parallel shift of the 45-degree line (slightly steeper, as expected based on Figure 4); and the linear fit for non-hematologic cancers is much more shallow in slope. Note that given the dearth of quasi-experimental evidence documenting that increases in pharmaceutical R&D translate into improved survival (see, e.g., Lichtenberg 2012), this evidence that the additional R&D investments induced by shorter commercialization lags (by relying

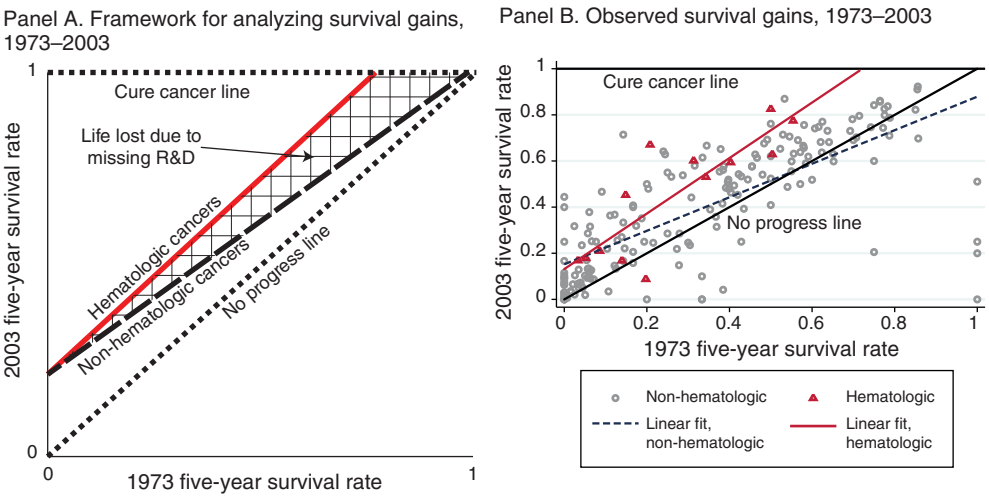

FIGURE 6. SURVIVAL GAINS, 1973–2003

Notes: This figure illustrates how we use variation in surrogate endpoints (across hematologic and non-hematologic cancers) to estimate counterfactual survival gains from 1973–2003 that would have been observed had commercialization lags for non-hematologic cancers mirrored the shorter commercialization lags realized for hematologic cancers. Panel A illustrates our conceptual framework. Panel B illustrates the empirical analog of panel A, plotting the 1973 five-year survival rate against the 2003 five-year survival rate. The level of observation is the cancer-stage. For details on the sample, see the text and online Data Appendix.

on surrogate endpoints) translated into improved survival gains is itself of substantive interest.[51]

The area between the linear fit line for hematologic cancers and the linear fit line for non-hematologic cancers can be used to quantify the number of life-years that would have been gained if commercialization lags for non-hematologic cancers had been similar to commercialization lags for hematologic cancers. We formalize this estimation for the cohort of US cancer patients diagnosed in 2003 as follows. First, on the sample of hematologic cancers, we predict the 2003 five-year survival rate as a function of the 1973 five-year survival rate. Second, for the sample of non-hematologic cancers we use the estimated β from the hematologic cancers survival regression to predict a counterfactual 2003 five-year survival rate for non-hematologic cancers had commercialization lags for non-hematologic cancers been similar to commercialization lags for hematologic cancers. Third, we calculate

[51] Welch, Schwartz, and Woloshin (2000) and others have argued that although five-year survival is a valid measure for comparing cancer therapies in a randomized trial, changes in five-year survival rates over time may be biased by changes in diagnosis patterns (known as "lead-time bias"). For example, an expansion in mammography screening between 1973 and 2003 could have led to breast cancers being diagnosed at an earlier stage, which would have mechanically increased measured five-year survival rates even if there was no real change in patient health. In our context, changes in diagnosis would be expected to bias us away from finding that hematologic cancers saw larger gains in survival between 1973 and 2003 because the cancers that saw increases in screening over this period (such as breast and prostate cancer) are non-hematologic cancers. Empirically, if we construct an alternative version of panel B of Figure 6 that plots the preferred outcome variable of Welch et al.—the percent change in mortality from 1973 to 2003—against the 1973 five-year survival rate, we observe a very similar pattern to that displayed in panel B: first, hematologic cancers on average had larger percent improvements in mortality from 1973 to 2003 than did non-hematologic cancers; second, as predicted by our model there is no gap between the hematologic and non-hematologic lines for patient groups with near-zero 1973 five-year survival rates; and third, the gap between the hematologic and non-hematologic lines increases in magnitude as the 1973 five-year survival rate increases. Taken together, these results suggest that changes in diagnosis patterns are not generating the differential patterns of survival changes across hematologic and non-hematologic cancers presented in panel B of Figure 6.

δ_{cs}, the difference between the counterfactual and actual 2003 five-year survival rates, for each non-hematologic cancer-stage; on average, δ_{cs} is 13.2 percentage points. Fourth, we convert each δ_{cs} into a number of life-years lost per person based on the fact that, in our data, a change from 0 to 1 in the five-year survival rate corresponds to a gain of 8.1 additional years of life. Applying this conversion, the average δ_{cs} of 13.2 percentage points corresponds to $(8.1)(0.132) = 1.07$ life-years per cancer patient. Fifth, we multiply each cancer-stage estimate of per-person life-years lost by the number of US cancer patients diagnosed in 2003 with that cancer-stage. We compute the number of patients in each cancer-stage using the SEER data, scaling up (dividing by 0.074) to account for the fact that SEER does not cover the entire US population. In total, this calculation suggests that among this cohort of patients—US cancer patients diagnosed in 2003—the longer commercialization lags required for non-hematologic cancers generated around 890,000 lost life-years.

If we value each lost life-year at $100,000 (Cutler 2004), the estimated value of these lost life-years is on the order of $89 billion per annual patient cohort. Applying a conservative social discount rate of 5 percent and assuming that patient cohorts grow with population growth of 1 percent, the net present value of the life-years at stake is $\$89\,\text{billion}/(0.05 - 0.01) = \$2.2\,\text{trillion}$.[52]

It is important to note that this life-lost estimate is rough at best. Our point estimate of the value of life lost per annual patient cohort is $89 billion, with a 95 percent confidence interval that ranges from $7 billion to $172 billion; the net present value point estimate of $2.2 trillion has a 95 percent confidence interval that ranges from $170 billion to $4.2 trillion.[53]

VI. Discussion and Conclusion

In this paper, we investigate whether private firms underinvest in long-term research projects. Our theoretical model clarifies how two factors—corporate short-termism and the structure of the patent system—may generate incentives that distort private research investments away from inventions that have both a long useful life and a long commercialization lag. We then investigate this distortion empirically in the context of the pharmaceutical industry, where drugs treating patients with short life expectancies can move through clinical trials more quickly than can drugs treating patients with longer life expectancies. Using a newly constructed dataset on cancer clinical trial investments, we provide several sources of evidence which together are consistent with commercialization lags distorting private R&D investments away from drugs to prevent or treat early-stage cancers.

We use our theoretical model to analyze the innovation and social welfare consequences of three policy interventions which could address this distortion: a policy change that would allow firms to rely on surrogate endpoints in clinical trials, a

[52] Note that other authors, such as Murphy and Topel (2006) and Weitzman (1998), have argued that a social discount rate of 2 percent or lower may be more appropriate; using such lower values would of course increase our estimate of the net present value of life-years at stake.

[53] To be conservative, we compute these confidence intervals using HC3 standard errors rather than robust standard errors, given the expected downward finite sample bias of robust standard errors in this small sample of hematologic cancers (see, e.g., the discussion in Angrist and Pischke 2009). The analogous 95 percent confidence interval using robust standard errors is $15 billion to $164 billion (a net present value range from $365 billion to $4.1 trillion).

patent design change that would start the patent clock at commercialization, and R&D subsidies targeting projects with long commercialization lags. While surrogate endpoints and targeted R&D subsidies would address the distortion regardless of the source, the patent design change only addresses the fixed patent term distortion.

Empirically, we document evidence, consistent with our theoretical model, that surrogate endpoints appear to increase R&D investments on innovations that would otherwise have long commercialization lags. We also use this surrogate endpoint variation to estimate counterfactual improvements in cancer survival rates that would have been observed if commercialization lags were reduced. We estimate that among one cohort of patients—US cancer patients diagnosed in 2003—longer commercialization lags resulted in around 890,000 lost life-years. Valuing these lost life-years at $100,000 (Cutler 2004) suggests that the estimated social value of the life-years lost in this one cohort of patients is on the order of $89 billion per year. This evidence suggests that, in the case of hematologic cancers, apparently-valid surrogate endpoints were effective in increasing R&D investments on innovations that would otherwise have had long commercialization lags, and that the resulting increases in R&D translated (in this case) into real gains in patient health. While much attention has been focused on the risks and costs of using surrogate endpoints that may imperfectly correlate with real improvements in patient health, our analysis is, to the best of our knowledge, the first attempt to use the historical record to quantify how the availability and use of a valid surrogate endpoint affected R&D allocations and patient health outcomes.

The example of the Framingham Heart Study is helpful in illustrating the potential value of surrogate endpoints. Heart disease is the leading cause of death in the United States, but since 1968 the age-adjusted rate of deaths from heart disease has dropped by 50 percent.[54] Although some of these gains are due to lifestyle changes, much of the decline in heart disease has been attributed to improved pharmacological preventives and treatments for cardiovascular disease, including the development of beta-blockers, ACE-inhibitors, and statins (Weisfelt and Zieman 2007). Patients use these drugs to reduce the morbidity and mortality from heart disease, but very few of these drugs reached the market based on clinical trials using morbidity or mortality as the endpoint. Rather, almost all were approved based on evidence that these drugs lowered either blood pressure or LDL (low-density lipoprotein) cholesterol—outcomes that can be measured much more quickly than morbidity and mortality (Psaty et al. 1999). These surrogate endpoints were first identified by the Framingham Heart Study, a large-scale, multi-decade, federally funded observational study which found that high blood pressure and LDL cholesterol are critical risk factors in cardiovascular disease. Subsequent clinical trials helped to validate these prognostic factors, which led the FDA to accept them as surrogate endpoints in cardiovascular trials (Meyskens et al. 2011). Researchers have argued that without these surrogate endpoints, it is unclear whether drugs such as beta-blockers, ACE-inhibitors, and statins would have reached the market as treatments for heart disease (Lathia et al. 2009; Meyskens et al. 2011). Note that public subsidies—such as federal support for the Framingham study—were likely important in this context,

[54] See, for example, the discussion in Cutler and Kadiyala (2003).

because any individual firm's investment in discovering and validating surrogate endpoints would generate benefits that largely spill over to other firms. Both our empirical evidence on the effects of surrogate endpoints for hematologic cancers and this historical case study for heart disease suggest that research investments aimed at establishing and validating surrogate endpoints may have a large social return.[55]

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[55] This type of argument has also been made informally by the cancer research community: see, for example, Korn and Stanski (2005); Institute of Medicine (2008); Lathia et al. (2009); and American Society of Clinical Oncology (2011). Collins (2012) provides an example of a technology—a chip that mimics how humans respond to a drug—that could serve the same role as a surrogate endpoint, by identifying promising candidate drugs more quickly.

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